SURGERY
GYNECOLOGY AND OBSTETRICS
An International Magazine, Published Monthly

VOLUME 72 APRIL, 1941 NUMBER 4

EXPERIMENTAL ANALYSIS OF THE GROWTH PATTERN AND RATES OF APPOSITIONAL AND LONGITUDINAL GROWTH IN THE RAT FEMUR

LEON J. ARIES, M.D., Ph.D., F.A.C.S., Chicago, Illinois

THE problem of bone growth has been studied for centuries and to the present day is not completely understood. From the earliest records, information has been gathered from purely morphological studies. The chief advances in the knowledge of bone growth have been made using the physiological method of vital staining. The purpose of this study was to investigate experimentally the growth pattern and assess quantitatively the rates of growth in long bones by the method of vital staining.

REVIEW OF LITERATURE

The foundation of our knowledge of the mode of bone growth began in 1736 when John Belchier (16), an English surgeon, was entertained at a dinner by a calico printer. The entree was roast pig and a joint of this pig was served to Belchier. The pink, ruddy color of the bones of this pork aroused the scientist's curiosity and he asked his host about the origin of the pig. The calico printer, being an economical man, used the madder-soaked bran from his dye vats to feed his pigs. The pigs he then used to feed to his friends. Subsequently, Belchier fed madder root to a cock forcibly and it died in 16 days. This single result of the pink color of the fowl's bones, he reported to the Royal Society (3).

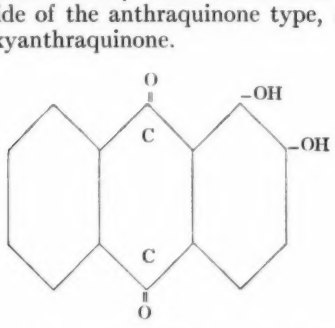
Henri Louis Duhamel fed madder to animals and then withdrew the dye. He observed that upon later sacrificing the animal, nearly all the redness was gone from the bone. This led him to believe that the stain was only temporary. When these bones were sectioned, he observed that the madder colored layer was covered and hidden by an unstained surface layer of bone laid down after the madder diet had been suspended. Duhamel then found by alternating madder diet with periods without madder he obtained red and white layers on the circumference of the bone. The last formed layer or plate was on the surface of the bone immediately under the periosteum. He concluded that bone grew as wood grew with superposition of layer upon layer. He also concluded that it was the periosteum that possessed the osteogenic function.

This method of vital staining with madder was not new although it was noticed by Belchier in 1736. It was known to the Greeks (11). The Egyptians brought madder from India where they learned the trick of combining it with calcium, aluminum salts, and polymerized fatty acids as mordants (18).

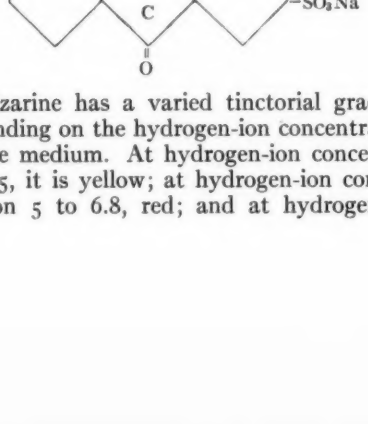
From the Division of Surgery, Northwestern University Medical School. Awarded the Chicago Surgical Society Prize for Research Completed in 1940.

Madder is a powdered root of Rubia cordifolia in India and Central Asia. In Europe, it is the Rubia peregrina (native wild plant) of England, Wales, and Ireland. The U. S. Dispensatory refers to it as Rubia tinctorum (23). The active principle of the madder root dye is alizarine and purpurin and its name was received from the trade name Levantine madder root (4). The dye occurs as a glucoside (ruberythric acid) in the roots in 2 to 4 per cent proportions and is obtained by fermentation or boiling with dilute acids. It is a reddish yellow powder insoluble in cold water and slightly soluble in boiling water. However, it dissolves in hot alcohol, ether, benzine, glycerine, or glacial acetic acid.

Alizarine was isolated from madder by Robiquet and Cobin in 1827 (5). Graebe and Lieberman in 1870 showed that it was a glucoside of the anthraquinone type, 1–2 dihydroxyanthraquinone.



Perkin (17), 1870, found the sodium sulphonate salt, alizarine red S which was more soluble and more stable than alizarine.



Alizarine has a varied tinctorial gradient depending on the hydrogen-ion concentration of the medium. At hydrogen-ion concentration 5, it is yellow; at hydrogen-ion concentration 5 to 6.8, red; and at hydrogen-ion concentration greater than 6.8, it is purple (4). The younger the age of the animal injected, the deeper is the color of the stain in the bones and teeth while old animals take the stain poorly or not at all. Thus, there is a selective staining of bone and teeth which are growing and calcifying at the time of injection.

TABLE I.—EXPERIMENTAL HISTORY OF 52 ALBINO RATS GIVEN INJECTIONS OF ALIZARINE RED S FROM 11 TO 299 DAYS OF AGE

Group No.	Arbitrary age range of animals in days	Number of animals allocated to each group	Age in days when injected	Interval between injection in days	Age when sacrificed
1	10–30	10	11–14–18–26	7–14–25 30–33	32–33–48 63–64–71
2	30–60	7	31–32–36–38 57	18–24–28 30–33–37	64–68–102 111–110 123
3	60–100	14	62–72–77–78 85–87–93–99	14–21–30 41–61–62	99–113–121 133–140 141–154
4	100–150	13	102–103–106 107–108–123 142–143	9–14–30 31–33–40 41–60	113–123 129–133 140–141 154–171 173–192 205
5	150–200	4	162–163–172	9–29–30 31–33–61	171–192 205
6	200–305	4	205–233–209	5–28–30 33–94–101	245–256 304–292

Hoffman (12) in 1939 demonstrated that the staining effect of alizarine red S in bones is dependent upon the hydrogen-ion concentration value of the colloidal matrix at moment the calcium precipitates to its earthen state.

Schour and Hoffman (13, 19–22) measured the appositional growth of the incisor and molar teeth in the rat, as demonstrated by alizarine red S. These workers injected the rat with alizarine red S at varying intervals and measured the amount of appositional growth over that given period. Their work opened a new field of research on growth of teeth and bones and directly suggested a similar study on rat femur.

METHOD AND MATERIALS

This study is based on the examination of 180 albino rats ranging from 7 to 304 days of age. Intraperitoneal injections of a 2 per cent isotonic alizarine red S solution, color index No. 1034, were given at intervals of 7 to 101 days. The pharmacological dosage was

experimentally found to be approximately 100 milligrams per kilogram (Hoffman and Schour, 19). The macroscopic and microscopic measurements were based on 52 animals (Tables I, II, III, and IV). Intravenous injection allowed for too rapid excretion of the dye before it could be deposited in the ossifying bone.

Number of injections. On the basis of preliminary trial animals, it was found advisable to limit the number of injections to one or two for each animal since more than two lines caused confusion as to which injection produced which line. For convenience, the animals were allocated into incremental age groups depending upon the days on which they were injected (Table I).

Dissection and the preparation of microscopic sections. The usual method of making microscopic sections of bone for histological study by decalcification in acid could not be employed in this experiment since the red to purplish effect of the alizarine red S in the bone is decolorized. Gross specimens were preserved in 10 per cent formalin to which magnesium carbonate had been added. After the bone was cleaned of all muscular and tendinous attachments, cut sections were prepared at the following levels: (a) through the neck and head; (b) transversely through the shaft, distal to the lesser trochanter; (c) transversely through the diaphysis; and (d) longitudinally, midsagittal mediolateral sections (Figs. 1 and 2).

The bone was cut with a 0.5 millimeter jeweler's saw blade which was mounted in an appropriate frame. One surface of the cut section was ground smooth on a circular fine grade carborundum stone attached to a laboratory lathe. This section was dehydrated in alcohol and treated with acetone. The smooth surface was fixed to the flat ground facing of a cork in cellulose cement. The cement served as an embedding medium and to attach the section to the cork. When the cement was completely set (4 hours), the exposed surface was ground to a thickness of 20 to 50 microns. While being ground, the bone was continuously cooled and washed free of débris by a stream of water passing through a brush placed against the stone. Final polishing of the section was completed on a hard Arkansas stone.

The bone was removed from the cork by immersion in acetone. Several changes in fresh acetone were necessary to free the sections of excess cellulose cement. The sections were then dried and cleared for 24 hours in xylol and mounted in gum dammar. It was found that the red stain faded and disappeared in several weeks from sections which were mounted in balsam. One half of the longitudinal section of the femur was ground and mounted as described while the opposite half was immersed in xylol for clearing. The cleared bones were examined with the aid of a binocular dissecting microscope while suspended in the clearing solution. The red stain could be studied from a three dimensional aspect.

Method of examination. Gross specimens were measured for length and diameters overall with a Boley gauge. Readings were made correctly to 1/100 of a millimeter.

Microscopic studies of the ground sections were made under the 32 and 16 millimeter objectives. A vernier filar micrometer eyepiece which was calibrated to a standard micrometer stage for the microscope and lenses, was used to make the measurements between the injection effects of the alizarine red S. Measurements were made in microns and were calculated correctly to within the first decimal place.

Measurements were made at the levels shown in Figures 1 and 2. The mean values, standard deviations, and error of the mean were calculated for the specific levels of animals within specific age groups (Table I).

The measurements of the means for each animal were plotted against time (Figures 5, 6, 7, 8), both arithmetically and logarithmically.

FINDINGS

Gross observations. Gross examination revealed a diffuse, purplish-red stain of the femur in animals injected with alizarine red S from birth to 15 days of age. Animals injected at 15 days of age and sacrificed at 30 to 60 days of age presented a diffuse, purplish-red stain in the metaphyseal portions of the bone and a colorless diaphyseal bone as well as a colorless subcapital segment. The junction of the colorless diaphysis with the shaft showed an intensely stained band which encircled the bone at that level (Fig. 3, left). The longitudinally

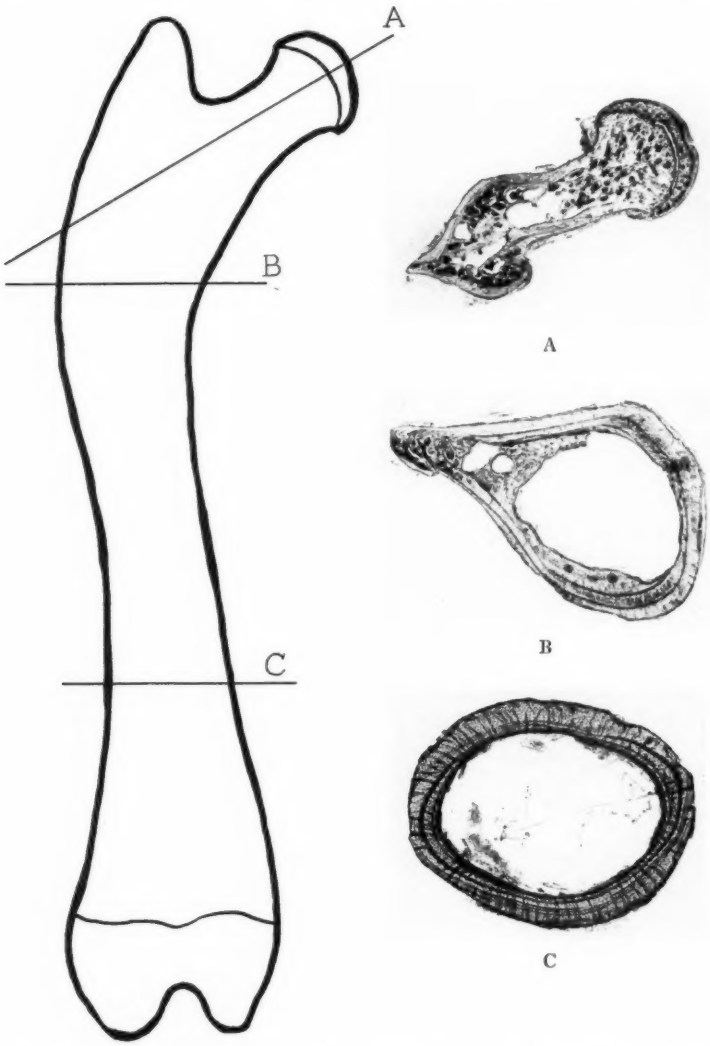


Fig. 1. Photomicrographs of transverse ground sections and levels at which they were made through the femurs of alizarinated rats. *A*, Longitudinal through head and neck and obliquely through the shaft distal to the greater trochanter. *B*, Shaft, just distal to the lesser trochanter. *C*, Diaphyseal end of shaft.

cut section (Fig. 2) of the bone presented a diffuse red stain in the medullary cavity, but the sharp differentiation between colorless diaphysis and stained shaft was not seen as a sharp line and faded gradually toward the distal end.

The circumferential colored lines on the surface of the cortex in the shaft of the bone were parallel to the epiphyseal plate and varied in their distance from the epiphyseal plate in approximately direct relation to the number of days intervening between injections. The animals which were given injections at varied intervals presented parallel colored rings about the shaft, the distance between which was the amount of longitudinal growth at the diaphyseal ends of the bone for that interval.

The longitudinal midsagittal sections (Fig. 4) presented oblique, red lines extending from the medulla of the shaft outward and toward

the epiphysis (Fig. 3 and 4) to end tangentially at the surface of the bone with the parallel lines mentioned. This would be at the epiphysis if the animal were injected and sacrificed within a few days. When 10 to 30 days elapsed between an injection and the time the animal was sacrificed, these oblique red lines were found at a distance away from the epiphyseal plate and ended at the periosteal surface red line (Fig. 4). This arrangement of a circular base with oblique lines beginning at the cortical margin and extending away from the epiphysis and medially formed a red truncated cone. The cleared femurs of animals which had been given one injection presented this picture in three dimensions when examined with a binocular dissecting microscope. When a second injection was given 30 days later the oblique red lines were found epiphyseally to the first line and were parallel to them. These oblique lines ended at the periosteal surface of the cortex where the red circular lines were found. The perimeter of the base of this cone formed the circumferential lines seen on the surface of the cortex (Fig. 3). Each succeeding injection line was found epiphyseally to the previous one in the form of one cone within another. The base was the epiphyseal plate but as more bone was deposited, the legs and the perimeter of the cone (Fig. 4) remained in the shaft as fixed planes. The base remained as the epiphyseal plate and did not take the alizarine stain.

Subsequent injections formed new cones which were seen to dovetail within the cones formed by the previous alizarine red S effects. The epiphyseal plate was now found to have receded from the levels of the initial alizarine red S rings (on the surface of the bone) and was approximately parallel to them.

The neck. Longitudinal sections through the neck (Fig. 1, *A*) included an oblique section through the shaft and lesser trochanter. The oblique endosteal red lines passed from the marrow cavity of the neck upward and outward toward the capital epiphysis. The periosteal deposit was found about the neck and was continuous with the red line in the trochanter and shaft (Fig. 1, A and 4). A morphological arrangement of the alizarine red S lines, similar to that of the distal end of the femur, existed in the neck. Similar truncated cones appeared superposed one within the other excepting that the base was proximal while in the condylar end of the femur the base of the cone was distal.

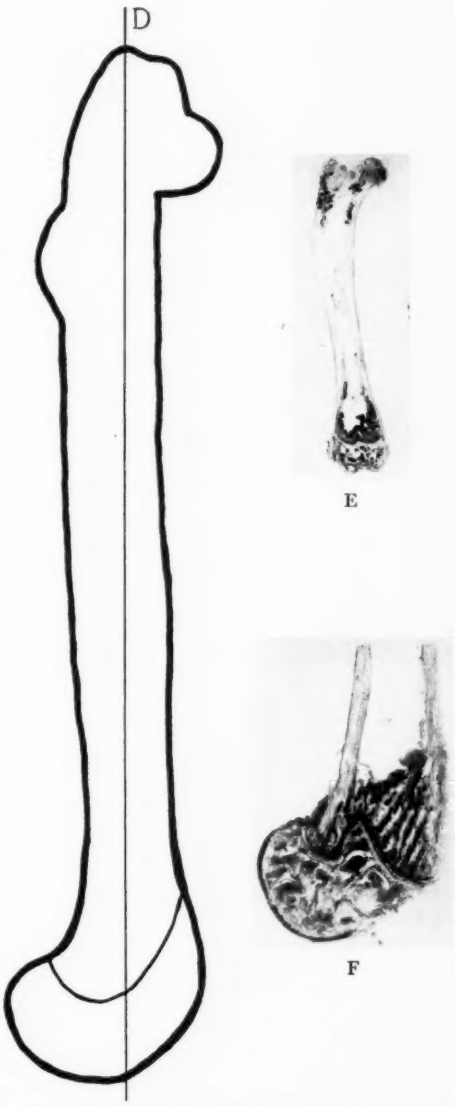


Fig. 2. *D*, Longitudinal midsagittal section through the shaft of the femurs of alizarinated rats. *E*, Mediolateral. *F*, Anteroposterior.

Fig. 3. Photograph of the femur of a 178 day old rat showing the effect of one injection of alizarine red S given at 87 days of age. Left, midsagittal longitudinal section of left femur showing alizarine red S effect in cortex. Right, Outer surface of the cortex of the right femur showing the alizarine red S effect at the proximal and distal end.

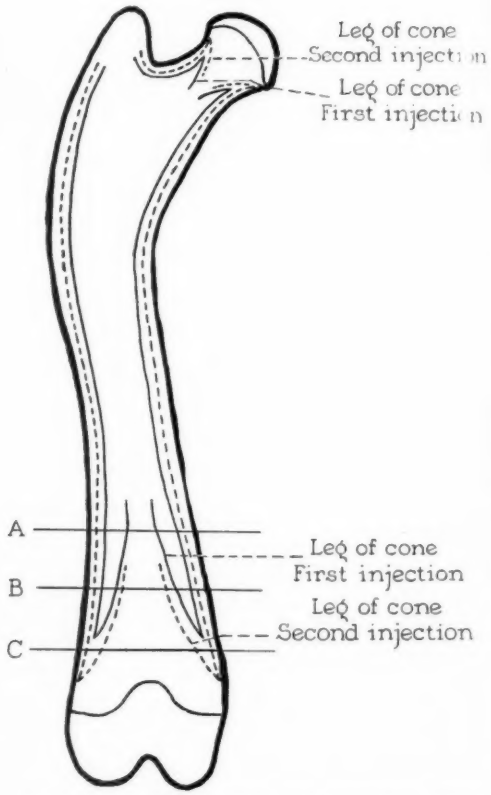


Fig. 4. Longitudinal section through femur showing two alizarine red S effects in a 150 day old animal. Solid line, first injection at 60 days of age. Broken line, second injection at 100 days of age.

Periosteal growth. Concomitant with the longitudinal growth of bone there was seen a subperiosteal deposition of bone about the entire shaft. This subperiosteal deposition of bone showed the alizarine red S effects. When viewed in cross section, circular red rings were seen to parallel the periphery of the bone. Cross sections through the shaft at the subtrochanteric level (Fig. 1, *B*) showed circular red lines in the cortex. The number of concentric lines at this level was directly representative of the number of injections given.

Transverse sections through the diaphysis presented three different findings dependent upon (1) level of diaphysis through which section was made, (2) number of injections, and (3) interval of time between injections.

When one injection was given one or two circular lines were found. When two injections were given, two, three, or four concentric red rings were seen (Fig. 4 *A*, *B*, *C*). The distance between the lines was not regularly equal as those found in the subtrochanteric region of the shaft. To clarify the discrepancy in the number of circular red lines found in the diaphysis as compared with the number of injections given, it was necessary to restudy the cleared sections. The junction of the red line of the cone on the inner surface of the shaft with the periosteal deposit showed two lines on cross section (Fig. 5, *C*). The solid black line indicates size of bone at time of first injection; broken line at second injection.

Haversian bone. The walls of the vascular channels in the haversian systems showed the

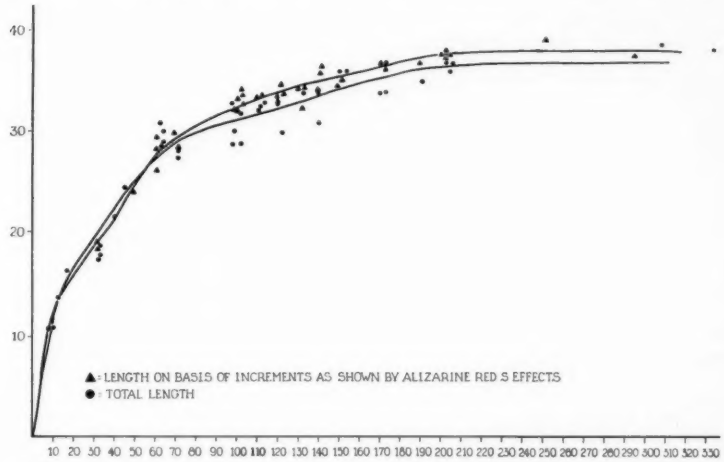


Fig. 5. Graph showing total lengths in millimeters and total longitudinal increments as shown by alizarine red S effects in the femurs of 52 albino rats from 11 to 364 days of age (From Table II).

alizarine red S effects in the arrangement of concentric rings. The concentric lamellae of the bone cells were parallel to these red rings. Bone growth within the haversian systems occurred as a result of deposition of new bone on the wall of the vascular channel and caused a diminution in the diameter of the channel.

QUANTITATIVE ASSESSMENTS

Longitudinal growth — gross. The lengths over-all of the femurs on the basis of 10 day

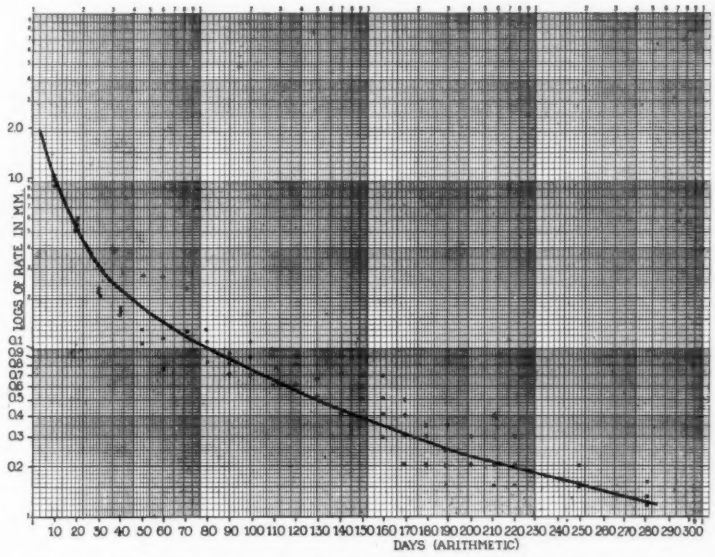


Fig. 6. Graph showing semilogarithmic representation of the daily rates of longitudinal growth in the rat femur from 10 to 304 days of age.

TABLE II.—TOTAL LONGITUDINAL INCREMENTS OF GROWTH IN THE FEMURS OF 52 ALBINO RATS FROM 11 TO 304 DAYS OF AGE

No. of rat	Age in days	Growth at distal end in mm.	Growth at neck in mm.	Length of femur at Age (in days)		Total length in mm.
151	32	4.2	1.04	13.4	18	18.6
132	40	2.1	0.40	17.6	26	19.2
150	48	4.32	0.80	19.2	32	24.3
148	48	3.90	0.80	19.6	33	24.3
105	63	3.75	0.53	24.3	48	28.58
127	63	3.00	0.54	24.3	48	27.84
106	64	3.84	0.53	24.3	48	28.67
106	64	6.72	0.78	19.2	32	26.68
135	63	4.60	0.80	24.3	48	29.70
104	71	3.91	0.69	24.3	48	28.89
105a	71	13.00	2.86	13.6	14	29.46
138	99	3.08	0.50	29.17	71	32.68
139	99	2.80	0.39	29.17	71	32.36
108	102	3.80	1.14	28.0	63	34.10
108	102	5.0	1.10	28.0	63	34.10
110	102	3.10	0.60	29.17	71	33.80
111	111	3.60	0.80	29.10	71	33.50
140	113	1.25	0.35	32.1	99	33.70
140	113	3.78	1.05	29.0	71	33.78
100	120	2.10	0.48	31.2	99	33.78
142	121	2.15	0.22	31.2	99	33.57
109	123	2.33	0.31	31.2	99	33.80
109	123	5.22	0.67	29.0	71	34.80
160	129	2.35	0.31	31.5	99	34.60
113	133	2.97	0.48	32.2	113	34.75
101	140	1.80	0.03	32.5	120	34.33
103	141	2.04	0.38	32.4	120	34.81
103	141	4.62	0.75	31.4	99	36.77
112	154	1.89	0.27	32.5	120	34.66
114	154	2.25	0.125	33	129	35.37
116	171	2.60	0.40	34.2	154	37.20
115	173	3.40	0.60	33.5	140	37.40
117	173	2.01	0.66	33.5	140	36.70
118	192	1.05	0.31	35.6	171	36.96
119	205	2.17	0.50	35.8	173	38.40
119	205	0.88	0.20	36.6	192	36.79
120	205	0.75	0.58	36.6	192	37.69
126	256	1.78	0.86	37.0	205	39.6
79	292	0.245	0.01	37.0	205	37.3

TABLE III.—CALCULATED DAILY RATES OF LONGITUDINAL GROWTH OF FEMURS FOR TEN DAY INCREMENTS

$$\text{Rate for any Period} = \frac{\text{Distance for period}}{\text{Time of that period}}$$

Days	Mm./Day	Days	Mm./Day
10	1.06	160	0.06
20	0.56	170	0.02
30	0.28	180	0.03
40	0.16	190	0.02
50	0.29	200	0.03
60	0.27	210	0.04
70	0.23	220	0.03
80	0.13	230	0.00
90	0.08	240	0.00
100	0.09	250	0.02
110	0.09	260	0.00
120	0.09	270	0.00
130	0.02	280	0.01
140	0.08	290	0.00
150	0.06	300	0.00

intervals from 10 to 300 days showed that the daily rates of growth decelerated with age increase (Table III, Fig. 6). These measurements closely coincided with similar data on longitudinal growth of the femur as shown by Donaldson.

Microscopic. Measurements which were made between the last two alizarine red S effects for specific age groups (Table I) showed that the increase at either the distal or the proximal ends alone was not equivalent to the total increase over-all for the femur at any given period. The sum, however, of the vertical increases at the distal and proximal ends closely coincided with the total increase over-all (Table II, Fig. 5).

Rates. The daily rates of growth, both experimental and calculated, as shown by the alizarine red S effects decelerated with age increase. The latter assessments of daily rates (sum of distal plus proximal) closely coincided with the calculated rates which were obtained from the curve on measurements of length over-all (Table II, Fig. 5).

Gradients. From the plotting of the decelerating rates on semilogarithmic graph paper (Fig. 6), it is evident that a gradient of growth

exists in the longitudinal growth of the rat femur. Logarithmic plotting of the total increments (Fig. 7) resulted in a straight line graph and also makes it evident that a gradient of growth exists (Huxley).

Subperiosteal growth. Measurements between injection effects in cross sections below the lesser trochanter showed that the distance between any two red lines was the amount of bone deposited for the given period at that level. The rates of growth were seen to be greater on the anterior than on the posterior surface (Table IV, Fig. 8). The growth of bone beneath the periosteum also decelerated with age increase for anterior and posterior surfaces (Table IV, Fig. 8).

Statistical evaluation on the basis of 1,034 trial measurements: The standard deviation was found to be 0.990 with a mean error of ± 0.249.

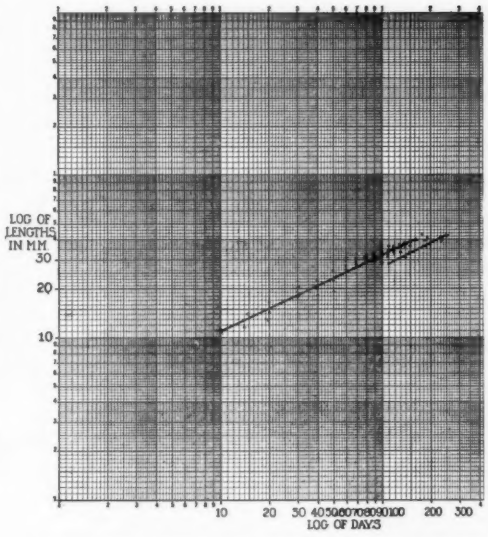


Fig. 7. Graph showing the logarithmic plotting of the increments of longitudinal growth in the femur of 52 albino rats from 11 to 304 days of age.

ANALYSIS OF STUDY

Pattern of growth. Textbooks of histology and embryology (1, 6, 15) have, to the present time, described the longitudinal growth of bone to take place by apposition at the diaphyseal side of the epiphyseal plate in the form of lines parallel to the epiphyseal plate. Our findings show the longitudinal apposition to be on the endosteal surface in the form of a cone whose base is the epiphyseal plate (Fig. 4, *A*). Multiple injections of alizarine red S have demonstrated that the appositional process results in a series of cones, each succeeding injection effect dovetailed within the previous. From a three dimensional aspect, it can be demonstrated that each successive endosteal deposit at the base (epiphyseal plate) possesses a greater perimeter than the previous one, and

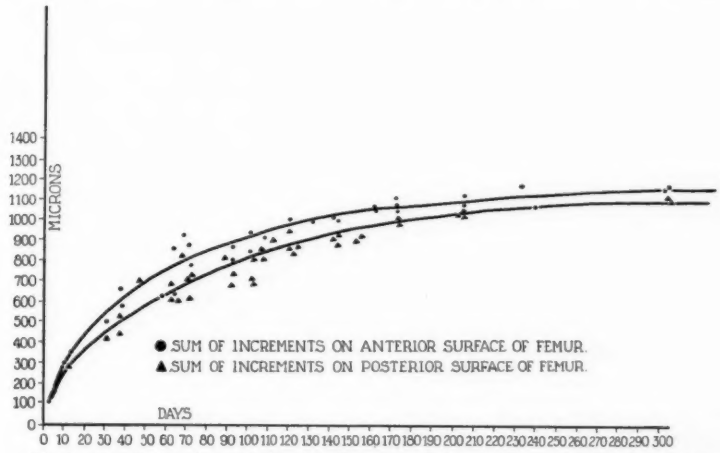


Fig. 8. Graph showing calculated daily rates of periosteal growth at the anterior and posterior surface of the femur just below the lesser trochanter in 52 albino rats.

TABLE IV.—CALCULATED DAILY RATES OF PERIOSTEAL GROWTH AT ANTERIOR AND POSTERIOR SURFACE OF FEMUR JUST BELOW LESSER TROCHANTER IN 52 ALBINO RATS

Age interval	Anterior		Posterior	
	Amount of growth in microns	Increase per day in microns	Amount of growth in microns	Increase per day in microns
10– 20	130.0	13.0	110.0	11.0
20– 30	120.0	12.0	80.0	8.0
30– 40	100.0	10.0	70.0	7.0
40– 50	90.0	9.0	60.0	6.0
50– 60	60.0	6.0	55.0	5.5
60– 70	40.0	3.0	65.0	6.5
70– 80	30.0	2.99	50.0	5.0
80– 90	29.9	2.99	35.0	3.5
90–100	29.5	2.90	35.0	3.5
100–110	29.0	2.80	40.0	4.0
110–120	28.0	2.40	30.0	3.0
120–130	24.0	2.20	25.0	2.5
130–140	22.0	2.20	20.0	2.0
140–150	20.0	1.99	25.0	2.5
150–160	19.9	1.60	20.0	2.0
160–170	16.0	1.58	15.0	1.5
170–180	15.8	1.51	15.0	1.5
180–190	14.3	1.43	15.0	1.5
190–200	12.0	1.20	15.0	1.5
200–210	10.0	1.00	10.0	1.0
210–220	9.0	.90	7.0	0.7
220–230	8.5	.85	8.0	0.8
230–240	7.0	.70	8.0	0.8
240–250	7.2	.72	7.0	0.7
250–260	6.8	.68	7.0	0.7
260–270	6.0	.60	6.0	0.6
270–280	5.5	.55	5.0	0.5
280–290	5.0	.50	5.0	0.5
290–300	5.0	.50	5.0	0.5

consequently produces a flare at the epiphyseal line. The latter accounts for the increasing flare at the epiphyseal end of the bone with advance in age. *As a result, there is a tubularization pattern in the growth of the long bones.*

The growth of the periosteal bone would, off-hand, appear to limit the pattern of bone to a straight cylinder with parallel walls. However, the periosteal growth follows the pattern of the internal cone and serves to increase the width of the cortex with increase in age. Preliminary assessments of periosteal growth on the same material have shown that the rate of growth is greater in the region of the shaft near the subtrochanteric area than at the diaphysis. Hence, approximately the total diameter of the bone at the epiphyseal line is due to the flare of the legs of the cone within the diaphysis (Fig. 4). This morphological pattern which is found at the distal end of the femur is also seen in the neck, though quantitatively to a lesser degree in the latter. The endosteal arrangement in cones as found in the femur was also found in the other long bones.

Mechanics of growth pattern. The structural growing pattern of the femur consists of two series of truncated cones with bases facing away from the shaft at both ends. The tibia at its proximal end presents a pattern similar to, and approximately a mirror image of, the growth pattern of the distal end of the femur.

Hence, on either side of the knee joint there is a series of truncated cones whose bases are separated only by the epiphysis of the femur and tibia, respectively. Weight is transmitted from the shaft of the femur to its wide distal base and received by the corresponding cap at the proximal end of the tibia.

Such an arrangement is one of the strongest geometric configurations known to engineering for weight support and serves for balanced equilibrium in force distribution. Columns with a cap and base are commonly employed by architects to support buildings.

Model. It was necessary to construct a transparent model of the femur to clarify in our minds the three dimensional effects of alizarine red S. The model was prepared by compressing a mixture of the monomer and polymer of methyl methacrylate (lucite) in a negative stone mold encased in a steel flask.

Lines of arrested growth. The peripheral base of each cone explains the so called Harris' "lines of arrested growth" (10). Harris has described these lines seen on x-ray films. Brash has superposed serial x-ray films of Harris' and has attempted to explain tubularization of bone on this basis. At present we are utilizing the alizarine red S method of vital injections to experimentally elucidate the significance of these "lines of arrested growth."

Outlook. The method for study of normal bone growth as described in this investigation may be readily employed in experiments dealing with studies (1) involving growth stimulating or growth arresting substances, (2) healing of fractures, (3) bone grafting, and (4) the fate of grafts, and other problems related to normal and pathologic conditions in bone.

SUMMARY AND CONCLUSIONS

1. This study was based on the gross examination and microscopic study of the ground longitudinal and cross sections of the femurs of 52 albino rats, 10 to 305 days of age, which were given multiple intraperitoneal injections of a 2 per cent solution of alizarine red S (100 milligrams per kilogram) at specified intervals. Quantitative assessments were made of the rates of longitudinal and subperiosteal growth. The pattern of morphological growth was analyzed as a result of the alizarine red S effects.

2. Findings show:

a. The longitudinal growth of long bones is a result of superposition of serial cones within the diaphyseal portion of the shaft, the bases of which cones are the epiphyseal plate at any given period.

b. The periosteum deposits bone on the circumferential surface of the shaft only and does not contribute toward the longitudinal growth of the femur.

c. The distal end of the femur grows faster than the proximal end (neck). The sum of the growth at both ends accounts for the total increase in length.

d. The longitudinal growth and the growth in width follows a growth gradient—the rates decelerating with increase in age.

e. Haversian system growth as shown by the alizarine red S effects occurs on the surfaces of the vascular canals. The red rings were seen to parallel the haversian lamellae. The diameter of the canals during appositional growth decreases with age.

3. The morphological pattern of the tubularization of bone is compared to mechanical supports as utilized in engineering and bears out the application of this mechanical arrangement to the knee joint.

4. Suggestions are offered for further investigation on normal and pathological studies on bone, utilizing the vital injections of alizarine red S.

BIBLIOGRAPHY

1. Arey, L. B. Developmental Anatomy. P. 302. Philadelphia: W. B. Saunders Co., 1930.
2. Belchier, John. Philos. hist. & mem. Roy. Acad. Sc. Par. abr., 1736, 39: 287–299.
3. Brash, J. C. Some problems in growth and developmental mechanics of bone. Edinburgh M. J., 1934, Pts. 1–41, 305–387.
4. Cameron, G. R. The staining of calcium. J. Path. & Bacteriol., 1930–1932, 33: 929.
5. Church. Chemistry of Paints and Paintings. 4th ed., 1915.
6. Cowdry, E. V. Textbook of Histology. Philadelphia: Lea & Febiger, 1938.
7. Donaldson, H. H. The Rat. Wistar Institute of Anatomy and Biology. P. 190. Philadelphia, 1924.
8. Duhamel, H. L. Memoire sur la garance et sa culture etc. Mém. Acad. roy. d. sc., 1739–1741, 1742–1743, Paris, 1757.
9. Graebe and Lieberman. Quoted by Cameron.
10. Harris, H. H. Bone in Health and Disease. New York: Oxford University Press, 1933.
11. Herodotus. Quoted by Cameron.
12. Hoffman, M. Personal communication.
13. Hoffman, M. M., and Schour, I. Rate and gradients of growth in rat molar as demonstrated by injections of alizarine red S. J. Dental Res., 1938, 17: 307–308.
14. Huxley, J. S. Problems of Relative Growth. New York: Lincoln MacVeigh, Dial Press, Inc., 1932.
15. Jordan, H. E. A Textbook of Histology. 5th ed. P. 72. New York: D. Appleton-Century Co., 1930.
16. Keith, A. Menders of the Maimed. Pp. 222–264. New York: Oxford University Press, 1919.
17. Knecht, Rawson, and Lowenthal. A Manual of Dyeing. 4th ed., 1917.
18. Pliny. Quoted by Cameron.
19. Schour, I., and Hoffman, M. M. Daily rhythm in rat incisor demonstrated by injections of alizarine. J. Dental Res., 1937, 16: 349.
20. Idem. Effect of alizarine red S injections on teeth and bones of Macacus rhesus monkey. Proc. Soc. Exper Biol. & Med., 1938, 37: 710–711.
21. Idem. Studies in tooth development, No. 2. The rate of apposition of enamel and dentine in man and other mammals. J. Dental Res., 1939, 18: 161–175.
22. Schour, I., Smith, M. C., and Hoffman, M. M. Effect of vitamin A deficiency on rate of apposition of dentine. Proc. Soc. Exper. Biol. & Med., 1938, 39: 447–450.
23. Wood, G. B. Rubia tinctorum. Dispensatory of the United States of America, 22nd ed. Philadelphia: J. B. Lippincott, 1937.

THE TENSILE STRENGTH OF SUTURED SKIN WOUNDS DURING HEALING

THOMAS W. BOTSFORD, M.D., Boston, Massachusetts

THIS investigation was undertaken to study the healing of uncomplicated and complicated incised skin wounds in animals. In these experiments the degree of healing was measured by determining *in vivo* the tensile strength of the wound, by the use of an apparatus which will be described later. Since the holding power of an incised wound, after the sutures have been removed, can depend upon little else than the degree of fibroplasia, the tensile strength should give an excellent index to the stage of healing. Uncomplicated incised wounds were observed to obtain a normal standard for this method of measurement. Wounds were opened and reclosed to obtain information on the value of secondary suture. Chromic catgut and silk were compared in another series of wounds, and the effect of avirulent bacteria as wound contaminants was studied. Finally, observations were made upon the value of splenic extract and embryonic extract in the healing of incised wounds of the skin.

Howes, Sooy, and Harvey (6) were the first to study wound healing as reflected by wound tensile strength. They made wounds in the skin, fascia, muscle, and stomach of dogs. The animals were sacrificed at varying intervals; the wounds were excised; and their tensile strength determined with a thread-testing machine. Later Harvey attacked the problem by making wounds in the stomach of the rat, and found the strength of the wound by inflating the viscus with air. In those experiments the workers demonstrated a standard curve for wound healing, which shows a quiescent period for the first 4 to 6 days, followed by a rapid gain in wound tensile strength until 10 to 14 days, when maximal wound strength is obtained. The latter stage is termed the phase of fibroplasia. It is of interest that Carrel had reached somewhat similar conclusions in his observations upon the diminishing surface area of open wounds.

From the Wilkie Surgical Research Laboratory, University of Edinburgh, Scotland.

George Gorham Peters Traveling Fellow in Surgery, Peter Bent Brigham Hospital, Boston, Massachusetts.

METHOD

A total of 77 adult guinea pigs and 11 adult dogs was used. The former were given all they could eat of a diet consisting of one-third whole bran, one-third cut hay, and one-third bruised oats. Green cabbage and water were given in unlimited quantity. The dogs received a stock diet of meat and scraps, with water as desired. The diets contained adequate carbohydrate, fat, protein, and vitamins for the requirements of these animals.

All wounds were made under ether anesthesia after preparation of the shaven skin with ether and iodine. Aseptic operating room technique was rigidly adhered to, and the wounds were dry before suturing. In the guinea pigs, two 3 centimeter wounds were made in each animal, one on each side of the spinal column approximately 1.5 centimeters from and parallel to it. Eight vertical 4 centimeter incisions were made on the abdomen of the dogs, distributed so that their blood supply was approximately the same. All wounds were through the skin and subcutaneous tissue only, and were closed with a single layer of interrupted untreated, 6½ pound tensile strength, silk sutures. The silk was sterilized by autoclaving 15 minutes at 20 pounds pressure. At end of operation a dry sterile dressing was applied.

The wounds were tested on various days after operation. In each guinea pig, both wounds were tested at the same time; and two more wounds were tested on the same day in each dog. When the wounds were to be tested, the animals were anesthetized with ether and the dressing was removed. A Michel skin clip 3 millimeters wide, or a small towel clip was then firmly clipped into the skin on each side at right angles to the approximate midpoint on the wound and about 1 centi-

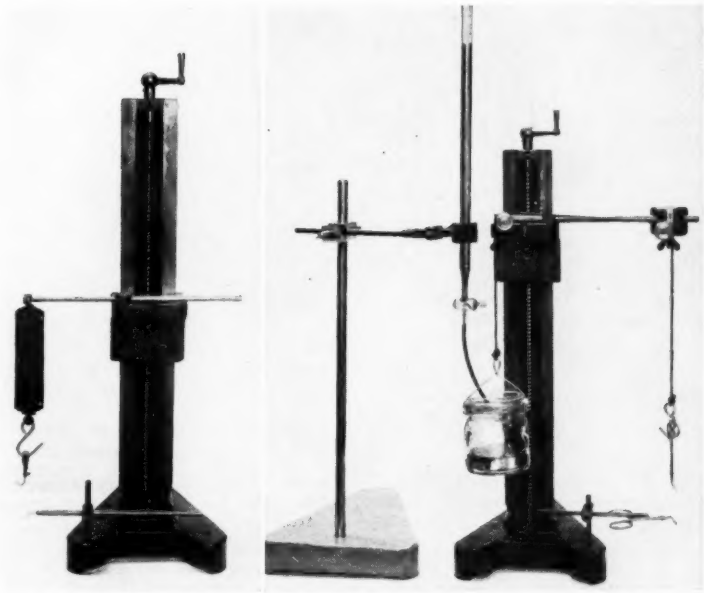


Fig. 1. Tensiometer for opening skin wounds, with spring balance.
Fig. 1a. Tensiometer with pulley and mercury bucket.

meter from it. The wound tensile strength testing apparatus pictured in Figure 1 was used. The hooks *A* and *B* (Fig. 2) were inserted through the loops of the skin clips. The wound sutures were now gently removed. The screw handle *C* (Fig. 2) was then slowly turned. This exerted constantly increasing tension upon the *A* side of the wound, whereas the *B* side remained fixed. The tension at which the wound gave was read directly from the spring balance *D* (Fig. 2). For wounds over a tensile strength of 1000 grams, a cord, a pulley, and a small bucket were substituted for the spring balance (Fig. 1a). Mercury was dropped into the bucket from a burette, and the total weight necessary to open the wound was easily calculated. When the test was finished, the wound was reclosed with sterile Michel skin clips. Infected wounds were not used except in the wound contaminant experiment. Whether this method of determining wound tensile strength *in vivo* is as accurate as that done with excised specimens is debatable. However, when wounds of similar size are tested in the same fashion each time, the error should be constant and the results consistent and accurate for comparison in a series. A total of 252 wounds was thus tested.

RESULTS

Group I. In this group the wounds were all uncomplicated, incised wounds sutured with fine silk. The curve of wound healing for 65 such wounds in guinea pigs is shown in Figure 3. The progress of healing, as measured by wound tensile strength, is slow but definite until the fourth day; thereafter there is a rapid rise in tensile strength until the tenth day, when the tensile strength remains more or less constant until the eighteenth day, which was the limit of the experiment. It is likely that in a given animal with 2 wounds made at the same time, the healing of the wounds should parallel each other, provided the blood supplies are equal and that infection is absent. In a series of 14 guinea pigs, each with two wounds, 8 of the animals had wounds that had tensile strengths within 100 grams of each other, while 6 showed a difference of 100 to 200 grams.

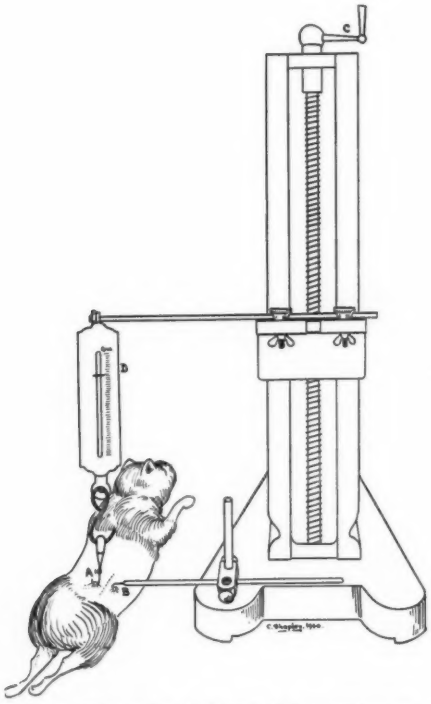


Fig. 2. Illustration of the use of the tensiometer.

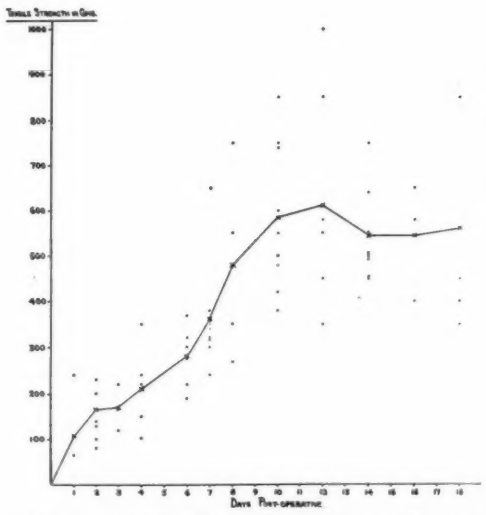


Fig. 3. Tensile strength of skin wounds in guinea pigs during healing. x—x, mean curve; .. .., individual wound strengths.

As seen in Figure 3, the animals tested on any particular day showed considerable variation in the tensile strength of their wounds, and this variation tends to increase as the mean tensile strength becomes greater. Thus, on the eighteenth day the readings varied from 350 grams to 850 grams, the range being 500, while on the first day the range was only 221 (19 gm. to 240 gm.). It might be anticipated that the range would be approximately proportional to the mean, and for this reason the coefficient of variation was calculated; this is the standard deviation S divided by the mean M. As the number of animals tested on any particular day was few, the standard deviation was computed for each day by the formula $S=\sqrt{\frac{\pm(X_R-M)^2}{n-1}}$ where X_R represents the separate readings X_1 ————X_n and n equals the number of readings. The average value of the coefficient of variation so calculated was found to be 0.71. An estimate was also made of the coefficient of variation for multiple wounds in single guinea pigs from animals that had two wounds each. The average value was 0.24. This is much less than that found for wounds in different animals, and it suggests that in guinea pigs, individuals show considerable differences with regard to wound healing which are much in excess of those shown by a single animal.

The curve for healing in 27 incised skin wounds in dogs is shown in Figure 4. The curve is of special interest for it is very similar to that reported by Howes, Sooy and Harvey from the determination of the strength of excised skin wounds in dogs. The gain in tensile strength is relatively slow until about the sixth day, when there is a rapid rise until the eighth day, and then a gradual gain in strength until the sixteenth day. Eight wounds in a single dog were tested in pairs at 4-day intervals for 16 days. None of the wounds was infected, and grossly they appeared much the same; however, the differences in the strengths of the wounds were striking (Table I). At each test, except the 4-day test, there was a difference in tensile strength ranging from 544 grams to 884 grams.

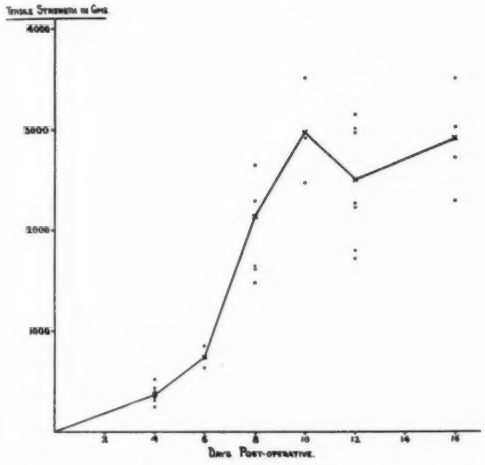


Fig. 4. Tensile strength of skin wounds in dogs during healing. x—x, mean curve; .. .., individual wound strengths.

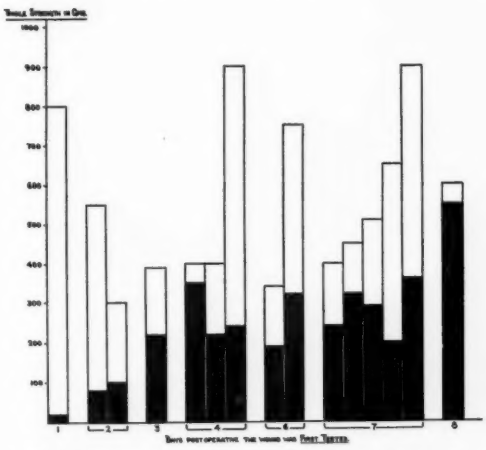


Fig. 5. Tensile strength of resutured wounds. All *re-tests* performed 7 days after the first test. Black columns, original strength of wound; white columns, strength of second test.

The variability in a single dog is of much the same order as in a single guinea pig, but differs from animal to animal. The coefficient of variation for wounds in a single animal was calculated from four pairs of wounds in one dog and was found to be 0.17. As this is derived from eight wounds, the standard error is considerably over 0.04 and does not differ significantly from the corresponding value of 0.24 found for guinea pigs. The coefficient of variation for different dogs was calculated to be 0.22, which is much less than the value for guinea pigs of 0.71. This means that the relative variation of tensile strength of wounds in dogs is only about one-third that found in wounds in guinea pigs. It is to be remembered that the actual strength of wounds in dogs is about five times that of guinea pigs, so that the range of tensile strength in grams is actually greater in the dog. It is, however, the relative strength that is important from a practical point of view, and this is brought out by the coefficient of variation.

It is obvious that in interpreting the results of any study of wound healing, this variation in the healing of multiple incised wounds in single animals, and from one animal to another, must be considered. It also follows that wound healing varies with species.

A number of wounds in guinea pigs, reclosed after the original wound test, were retested 7 days after the secondary closure of the wounds. The gains in wound strength over the original strength after secondary wound closure are shown in Figure 5. This demonstrates that resutured wounds are stronger. In only two wounds (not shown on the chart) were the tensile strengths less than the original; both of these wounds were infected. The increase in tensile strength of these secondarily closed wounds varied a great deal, and did not bear any definite relation to the original strength of the wound.

TABLE I.—VARIATION OF TENSILE STRENGTH IN MULTIPLE WOUNDS OF A SINGLE DOG

Post operative day of wound test	No. of wounds in dog	Tensile strength of wound in grams	Difference in grams	Coefficient of variation
4	1	350	50	.09
	2	400		
8	3	2286	686	.24
	4	1600		
12	5	3143	884	.23
	6	2259		
16	7	3006	544	.11
	8	3550		

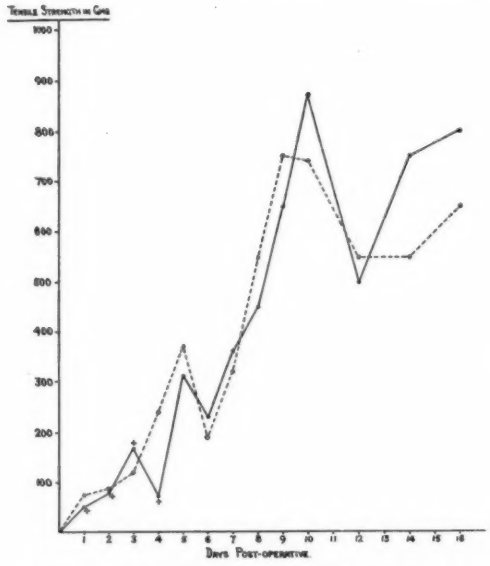


Fig. 6. Tensile strength of skin wounds in guinea pigs, contaminated with Staphylococcus albus. .—., wounds inoculated; o—o, control wounds; +, positive culture from wound.

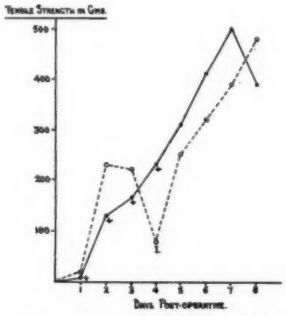


Fig. 7. Tensile strength of skin wounds in guinea pigs, contaminated with Bacillus subtilis. .—., wounds inoculated with Bacillus subtilis; o—o, controls; +, positive culture from wound; I, infected control wound.

It is worth noting that the strongest wounds in the guinea pigs were in this group of wounds retested seven days after being opened.

Group II. Because of the interest in causes of postoperative wound complications, the effect of avirulent bacteria as wound contaminants was studied. While these organisms usually do not cause wound suppuration, it was desired to find out if they have any effect upon the wound tensile strength. One wound in each of 13 guinea pigs was heavily inoculated with a 48 hour old dextrose broth culture of Staphylococcus albus, and in 8 guinea pigs a similar culture of Bacillus subtilis was used. These organisms were cultivated from room air. There was one control wound in each animal. Cultures were taken before operation from the skin and again from each wound as it was opened by the tensiometer. In 5 instances the pre-operative skin culture was positive for Staphylococcus aureus. Only one wound in this group became infected and that was a control wound. A mixed culture of Staphylococcus aureus and Bacillus proteus was obtained. In both groups of guinea pigs, the contaminant was recovered by culture from the inoculated wound on every day from the first to the fourth day; thereafter no organisms could be obtained by culture. In both the experiments the inoculated wounds were slightly stronger than the control wounds, although there was not much to choose between the control and contaminated wounds (Figs. 6 and 7). It would appear that mild wound infection has a favorable effect upon wound tensile strength. It is of interest to note the low tensile strength of the infected control wound (Fig. 7).

Group III. In a series of 14 guinea pigs, one wound was sutured with two interrupted, No. oo (Brit. Pharm.), 20 day chromic catgut sutures, while another wound in each animal was closed with two interrupted fine silk sutures. When the results given in Figure 8 are compared, it is suggested that the catgut is slightly superior to the silk for the first 4 days, but inferior on subsequent days. In the light of the great variability of wound healing in normal wounds, it would seem desirable to examine the figures from a statistical point of view. By use of the coefficient of variation (0.24) for two wounds in 1 animal, an estimate was made of the standard error of the differences of the two wounds in each animal, and from this the probability, P, was obtained that the differences greater and equal to the observed ones should have occurred by chance. The value, P, however, was found to be less than $1/50$, which confirms the conclusion that the differences between the

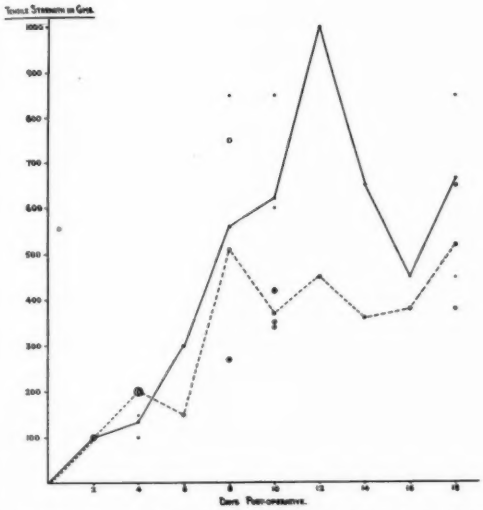


Fig. 8. Tensile strength of skin wounds in guinea pigs, sutured with silk and with catgut. .—., silk mean; o—o, catgut mean.

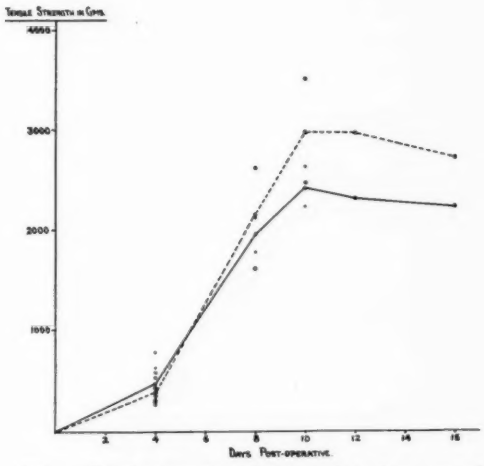


Fig. 9. Tensile strength of skin wounds in dogs, treated with epicutan. .—., mean of wounds treated with epicutan; o—o, mean of control wounds; . .oo, individual wound strengths.

wounds sutured with catgut and silk, respectively, are real. This is further supported by the fact that of the 11 animals examined from the fourth day onward, everyone agreed, in that the wound closed with silk was superior in strength to that sutured with catgut. Assuming equal chances of catgut or silk appearing superior in any animal, the chance of the whole 11 agreeing is $\frac{1}{2}^{10}$ or approximately 1 in 1000. The conclusion would seem justified that, after 4 days, skin wounds sutured with silk were less easily ruptured than those sutured with catgut in guinea pigs.

With regard to the fourth day (Fig. 8), the observations are limited to 2 animals, but in both of these the catgut wound was stronger than the silk wound. Further examination of the figures suggests that this result is in fact a significant one, but it is inadvisable to be dogmatic in view of the small number of animals.

Group IV. Recent reports by Nielson and Waugh have indicated that an embryonic extract developed by Dr. Albert Fisher, of the Carlsberg Biological Institute, Copenhagen, is of value in accelerating the healing of open surface wounds both in man and in experimental animals. These workers measured the diminishing area of the open wounds, and, by using du Noüy's mathematical equation by which the rate of healing might be expressed and its normal course predicted, concluded that the preparation accelerated the healing by about 30 per cent. The preparation[1] of embryonic extract referred to is known as "epicutan" and is a protein derivative of embryonic tissue absorbed in kaolin powder (8).

Because of the foregoing work, it was thought to be of interest to determine the effect of epicutan upon wound tensile strength. Accordingly, the preparation was dusted into 12 wounds in dogs. There was one control wound for each treated wound. When the results are considered in Figure 9, it is at once apparent that epicutan has no appreciable effect upon wound tensile strength. The preparation is recommended for open surface wounds, and it might be said that this is not a fair trial.

Group V. An extract of animal spleen was prepared by Dr. J. N. Davidson, physiology department, University College, Dundee. This splenic extract was applied to wounds in guinea pigs and dogs to determine whether it had any effect upon the acceleration of wound healing.

[1]Manufactured by Messrs. Lundbeck, of Copenhagen, under direction of Dr. Fisher.

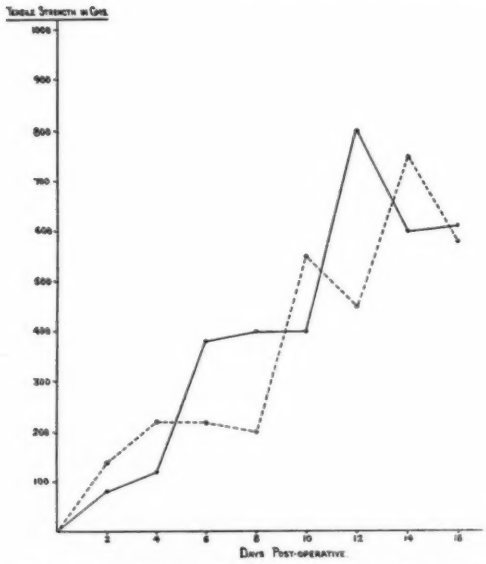


Fig. 10. Tensile strength of skin wounds in guinea pigs, treated with splenic extract. .—., wounds treated with splenic extract; o—o, control wounds.

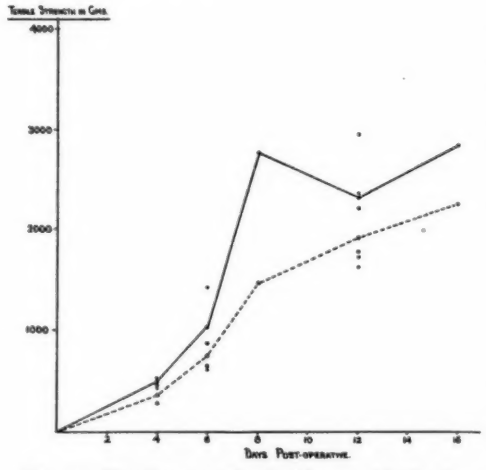


Fig. 11. Tensile strength of skin wounds in dogs, treated with splenic extract. .—., wounds treated with splenic extract; o—o, control wounds; ..oo individual wound strengths.

A consideration of the results from wounds in 8 guinea pigs (Fig. 10) shows that there was little difference between the treated and the untreated wounds, except that the splenic extract treated wounds did reveal a tendency for a gain in tensile strength to be more rapid than in the control wounds. The treated wounds in dogs, however, did show a difference from the untreated wounds (Fig. 11). In 2 instances the control wound was stronger than the extract treated wound, while in 8 instances the reverse was true. When one performs a statistical analysis of these figures, one finds that this figure (8 out of 10) cannot be regarded as very significant. The same conclusion is arrived at by the use of the coefficient of variation to calculate the expected variation by pairs and compare those with the differences actually observed. There is about one chance in twenty-five of differences equal or greater than the observed arising. We may conclude that the experiments in the case of the dog wounds suggest that the application of splenic extract promotes wound healing as measured by the tensile strength of the wounds, but further work is required to prove that fact.

ANALYSIS OF STUDY

There is little indication for generalizations on experiments such as the foregoing, for they have to be evaluated on their face value; and it is also to be remembered that they are on animals and not on man. It is, however, of interest to point out again the important factor of variation in healing in individual animals, and in animals with multiple wounds. This is knowledge that is of paramount importance in any study of wound healing. The factor of variation should hold true for open wounds as well as for incised wounds.

The gain in tensile strength of secondarily closed wounds coincides with the clinical experience of many (4) that disrupted wounds heal remarkably well if the patient survives. The fact that the contaminated wounds did well and the organisms disappeared rapidly is not salve for the surgeon's conscience, but merely another indication of nature's ability to protect.

Catgut versus silk has long been a subject of dispute between the advocates of each. Here silk was shown to be superior to catgut as a skin suture in guinea pigs. The actual tensile strength of the suture material did not enter as the sutures were removed before the wounds were tested. The reaction of the tissues to cat-

gut, which has been demonstrated by others (3) to be greater than that to silk, must be the underlying cause for the superiority of silk. This reaction, which is an exudative one, presumably delayed the onset of fibroplasia in these wounds.

The question of substances that may accelerate the healing of wounds is of perennial interest to the surgeon. The embryonic extract epicutan produced negative results as judged by the tensile strengths of the wounds concerned; but the trial of splenic extract in dogs was very suggestive of a beneficial action upon wound healing. This was not true in guinea pigs. Whether it is wise to attempt to accelerate the healing of incised wounds is a debatable point. In view of the variation in the healing of wounds in animals, an unstable wound might be the result. The unknown factor in each individual, which is the inherent ability to repair damaged tissue, is more important than substances which accelerate wound healing when applied locally. This does not intend to imply that local treatment of wounds is not essential, but means that nature should be helped but not pushed. This conception is based upon observations on incised wounds; and it would not be wise to apply it to open surface wounds. Additional work on this subject will be necessary in order to clarify the problem.

SUMMARY

1. A method for testing the tensile strength of wounds in animals *in vivo* is reported.

2. Normal curves of wound healing, as measured by the wound tensile strength of skin wounds *in vivo* in guinea pigs and dogs, are demonstrated.

3. The variation of the ability to heal among single animals and in the individual animal with multiple wounds is shown.

4. Experiments showing the value of secondary suture are described.

5. The superiority of silk over catgut as a skin suture is demonstrated.

6. Embryonic extract epicutan was found to have no effect, good or bad, upon wound healing as measured by wound tensile strength in dogs.

7. Splenic extract was found to be of questionable benefit in the acceleration of wound healing as measured by wound tensile strength in dogs.

I wish to record my thanks to Professor J. R. Learmonth for his advice and guidance in carrying out this work, and to acknowledge my indebtedness to the technical staff of the Wilkie Surgical Research Laboratory for their help. I also am indebted to Dr. W. O. Kermack of the Royal College of Physicians' Laboratory, Edinburgh, for his aid in the statistical analysis.

BIBLIOGRAPHY

1. Carrel, Alexis. The treatment of wounds. J. Am. M. Ass., 1910, 55: 2148.
2. du Noüy, P. L. General equation for the law of cicatrization of surface wounds. J. Exper. Med., 1919, 29: 329.
3. Halsted, W. S. The employment of fine silk in preference to catgut and the advantages of transfixing tissues and vessels in controlling hemorrhage. Surgical Papers, The Johns Hopkins Press, 1924, 1: 29–46.
4. Hartzell, J. B., and Wenfield, J. M. Disruption of abdominal wounds. Internat. Abst. Surg.. 1939 68: 585.
5. Harvey, S. C. The velocity of the growth of fibroblasts in the healing wound. Arch. Surg., 1929, 18: 1227.
6. Howes, E. L., Sooy, J. W., and Harvey, S. C. The healing of wounds as determined by their tensile strength. J. Am. M. Ass., 1929, 92: 42–45.
7. Nielson, E. The influence of animal growth substance upon the course of wound healing. Ugesk. f. Laeger, 1939, 37: 1071.
8. Waugh, W. G. Experiments in the acceleration of wound healing. Brit. M. J., 1940, Feb. 17, No. 4128, 249.

MALIGNANT LESIONS OF THE CECUM AND ASCENDING COLON

CHARLES W. MAYO, M.D., F.A.C.S., and W. RANDOLPH LOVELACE, II, M.D.,
Rochester, Minnesota

RESECTION of the right half of the colon, including the cecum, is the surgical procedure of choice in a variety of pathological conditions which affect this particular segment of the intestine. The most common of these is a malignant lesion.

The basis for this study is a series of 885 cases of malignant lesions of the cecum and ascending colon in which operation was performed at the Mayo Clinic in the years 1907 to 1938, inclusive.[1] These constitute about 80 per cent of all the malignant lesions of the cecum and ascending colon seen in this period. Cases in which the lesion was situated in the hepatic flexure of the colon were included but not those in which the lesion was distal to the hepatic flexure. In 358, or 40 per cent, of the cases the lesion was situated in the cecum, and in 527, or 60 per cent, it was situated in the ascending colon, including the hepatic flexure.

In 295 of the 885 cases, or 33 per cent, the operative procedures performed were not curative in purpose; they included, for instance, exploration and biopsy, palliative ileocolostomy, cecostomy, and ileostomy. Also included in this group are a few cases in which palliative resection was performed in the presence of extensive metastatic involvement of the lymph nodes or liver.

In 590, or 67 per cent, of the 885 cases, resection was performed with a view to cure. This is worthy of note because nonpalliative resection is attempted in only about 50 per cent of cases of malignant lesions of the left half of the colon in which surgical treatment is employed. In 247 of the 590 cases the lesion was situated in the cecum and in 343 cases it was in the ascending colon.

From the Division of Surgery, the Mayo Clinic.

Read before the meeting of the Western Surgical Association, Los Angeles, California, December 15 and 16, 1939.

[1]The statistical calculations included in this study were made under the auspices of the Division of Biometry and Medical Statistics of the Mayo Clinic.

The percentage of surgical cases of malignant lesions of the cecum and ascending colon in which nonpalliative resection could be attempted has remained rather constant in the 32 years covered by this study, although in the past 5 years there has been about a 3 per cent increase in the cases in which this was possible. This may be accounted for not only by earlier diagnosis but also by improvements in auxiliary surgical technique.

In order to determine the relative frequency of malignant lesions of the cecum and ascending colon and of other segments of the large intestine, we studied the histories of all cases in which operation for malignant lesions of the large intestine, including the anal canal, was performed at the clinic in the years 1907 to 1938, inclusive. The cases in which the lesion involved the cecum or ascending colon comprised 30 per cent of the cases in which the involvement was proximal to the termination of the sigmoid and 12 per cent of the entire group of cases.

This review is based on the summation of the operative experience of a rather large group of different surgeons. However, the group was thought to be sufficiently homogeneous to permit us to make a detailed statistical study of certain aspects of the problem.

AGE AND SEX

In this series of cases the age incidence was somewhat similar to that of carcinoma situated elsewhere in the body (Table I). In 20, or 2.3 per cent, of the 885 cases the patients were less than 30 years of age; in 14 of the 20 cases the lesion was in the cecum.

The impression of the surgeon that carcinoma which affects young people is more malignant than that which affects old people was supported by the results of a calculation of the 5 year survival rate. For the patients less than 40 years, the 5 year survival rate was

54 per cent and for the older patients it was 58 per cent. Deaths from all causes are included for these calculations. Since older people have a general death rate higher than younger people, correction should be made for the higher rates of the older people from other causes than cancer, if the true contrast so far as cancer is concerned is to be seen. When these survival rates were corrected for the normal death rates from causes other than cancer in the respective age groups, the 5 year survival rate for patients less than 40 years, exclusive of deaths from other causes than cancer, was found to be 55 per cent, and that for the patients 40 years or more of age was 66 per cent. This indicates a greater virulence of malignancy among the younger group.

TABLE I.—AGE AND SEX OF PATIENTS TREATED SURGICALLY DURING 1907 TO 1938, INCLUSIVE

Age, years	Lesion in cecum		Lesions in ascending colon	
	Patients	Per cent	Patients	Per cent
0– 9	1	0.3	0	
10–19	5	1.4	0	
20–29	8	2.2	6	1.1
30–39	33	9.2	54	10.2
40–49	69	19.3	101	19.2
50–59	117	32.7	151	28.7
60–69	99	27.7	173	32.8
70+	26	7.3	42	8.0
Total	358	100	527	100
Youngest patient	6 years		23 years	
Oldest patient	79 years		84 years	
Mean age	53.7 yrs.		55.2 yrs.	
Males	218	60.9	330	62.6
Females	140	39.1	197	37.4

RELATION OF MORTALITY RATE TO THE SURGICAL PROCEDURE

The gross hospital mortality rate for the entire series of 885 cases was 23.5 per cent. These cases include those in which only a palliative procedure was carried out as well as those in which it was possible to carry out resection with the object of cure. All deaths in the hospital are included, regardless of the cause of death or the time that had elapsed since operation.

In general, which is safer, a one stage or a two stage resection of the cecum and ascending colon? Most surgeons consider a two stage operation the safer procedure from the standpoint of operative mortality, and statistics from various hospitals and clinics seem to bear this out. Ransom recently reported a mortality rate of 32 per cent for one stage resection, in contrast to a mortality rate of 20 per cent for two stage operations. Allen (1, 2) reported a mortality rate of 20.5 per cent for one stage resection in 73 cases of carcinoma of the right portion of the colon and a mortality of 11 per cent in 18 cases in which a two stage procedure was performed.

Pemberton and Whittaker reported a series of 46 consecutive cases, in 8 of which single stage procedures were performed and in 38 of which two stage procedures were performed. In addition to the 46 cases, there were also 5 cases in which ileocolostomy was performed as the first part of a two stage operation. In the 38 cases in which the two stage resection was performed there were 2 deaths, a mortality rate of 5.2 per cent; there were 2 deaths in the 5 cases in which ileocolostomy only was performed as the first of a two stage procedure. In the total group of 43 cases in which two stage resection was contemplated, the mortality was 9.3 per cent. In the 8 cases in which a single stage operation was performed, there was 1 death. With good reason, Pemberton is an advocate of the two stage method of resection of the right half of the colon.

Harvey, however, advocated the one stage procedure and, in 1934, reported 18 cases of carcinoma of the cecum in which operation was performed with a mortality of 11 per cent. Stone and McLanahan (1939) advocated a one stage procedure whenever possible and also an aseptic type of end-to-end anastomosis. Jones advocated the use of an end-to-side anastomosis when a one stage resection is carried out. Lahey advocated a modified Mikulicz procedure with staggering of the proximal portion of the ileum for removal of malignant lesions in the right portion of the colon. He said that this type of operation obviated the danger of leakage and peritoneal contamination.

One of the most important advantages of one stage as compared to the two stage resection of the colon in cases of neoplasm in our opinion concerns the factor of time. It is reasonable to suppose that the longer a malignant lesion remains in the body, the greater is the risk of extensive metastasis which will preclude resection.

One of us (C. W. M.) has performed one stage resection of the right portion of the colon in an all inclusive series of 49 cases up to and including 1939, with a hospital mortality rate, figured regardless of time or cause, of 12.2 per cent. In the same period of time, a two stage resection was performed in 8 cases; in this group 1 death occurred after completion of the second stage of the operation and 2 deaths occurred following an ileotransverse colostomy. In fairness to the two stage resection, however, it must be stated that in the cases selected for this type of operation the condition was more serious, an important point to be kept in mind.

Until the present report, no large series of cases of malignant lesions of the cecum and ascending colon has been presented for comparison as to operative procedures and results. Of course, a review of such a large series as is included in the present report is made possible only by including the experience of several surgeons who have differed among themselves as to the advantages of different types of operations. It does not take into account the advantages of improved pre-operative and post-operative care characteristic of recent years. In the 590 cases in which operations were carried out with a view to cure, there were 315 in which a one stage resection was performed, 246 in which a two stage procedure was utilized and 29 in which more than a two stage procedure was employed. A review of the hospital mortality for this entire group would seem to indicate that the one stage resection has an advantage over the two stage procedure as the one stage resection resulted in a hospital mortality of 22.2 per cent as compared with a hospital mortality rate of 28.9 per cent for the two stage procedure, 15 per cent after the first stage and 13.9 per cent after the second stage. In the group of 29 cases in which resection was performed in more than two stages, there were 10 deaths in the hospital.

No case in which death has occurred in the hospital has been eliminated, regardless of how long after the operation it occurred or the cause of death. There is no intention in presenting the general mortality figures to deprecate any individual's surgical method because it is evident that the individual surgeon may master a method and obtain results which will justify the method, in spite of what may appear to be a condemnation in the general picture.

In considering the hospital mortality rate for one stage operations from the viewpoint of type of anastomosis, it was found that the hospital mortality rate was 22.7 per cent in cases in which a side-to-side anastomosis was done, 23.4 per cent in cases in which an end-to-side anastomosis was performed, and 19.2 per cent in cases in which an end-to-end anastomosis was done. Because of the technical difficulties, it is often impossible to carry out an end-to-end anastomosis, but it apparently is the procedure of choice when it can be accomplished. Comparison of the 5 year survival rates for the one stage and two stage types of resection showed a small advantage in favor of the one stage type after 5 years, even with the hospital mortality disregarded. The 5 year survival rate in cases in which the one stage procedure was used was 57.8 per cent as compared with 55.3 per cent for the two stage. Although the difference is small and must be viewed as tentative until an even larger series of cases can establish the survival rates, it is interesting that in this total series of cases the one stage operation is advantageous both so far as the immediate hospital mortality is concerned and also so far as the 5 year survival of those who withstood the operation successfully is concerned.

A review of the hospital mortality according to the age of the patient confirmed the general impression that mortality is very definitely greater as the age of the patient increases. While the hospital mortality for the whole group of patients who were subjected to operation with a view to cure was 25.6 per cent, that for the individuals less than 40 years of age was only 14.7 per cent, that for

individuals between 40 and 60 years was 21.0 per cent, while the mortality rate for individuals more than 60 years of age was above the average rate and increasingly so for individuals more than 70 years of age. In cases in which the value for the hemoglobin was less than 7 grams per 100 cubic centimeters of blood the mortality rate was 36.8 per cent; in cases in which the value was between 7 and 12 grams the mortality rate was 28.1 per cent, and in cases in which the value was more than 12 grams the rate was 22.3 per cent. Similarly, in cases in which the erythrocyte count was less than 3.5 million per cubic millimeter of blood the mortality rate was 39.5 per cent, as contrasted with a mortality of 16.7 per cent in cases in which the erythrocyte count was more than 4.5 million. In 97 patients in whom there was a perforating lesion, the mortality rate was 29.9 per cent, this as contrasted with a mortality rate of 24.7 per cent in those patients in whom perforation had not taken place.

MORBIDITY ASSOCIATED WITH ONE STAGE AND TWO STAGE RESECTION

In cases in which a one stage operation was performed 49 per cent of the patients spent a total time of less than 20 days in the hospital and 43 per cent spent between 20 and 35 days; the average was 21 days. In cases in which a two stage resection was performed, 22 per cent spent a total of between 20 and 35 days in the hospital and the rest spent more than 35 days in the hospital; the average was 45 days. Only 8 per cent of patients subjected to a one stage resection were in the hospital more than 35 days; 78 per cent of those who underwent a two stage procedure spent this length of time in the hospital. In addition, one must also consider the fact that in more than half of the cases in which the two stage procedure is used the patients must spend time, sometimes a considerable period, in the hospital between the first and second stages of the operative procedure. In the cases in which a two stage resection was performed, 13 per cent of the patients were out of the hospital for 20 to 34 days between the stages and 13 per cent were out of the hospital for 35 days or more.

THE QUESTION OF ILEOSTOMY

It often has been stated that an ileac stoma made proximal to the site of anastomosis acts as a safety valve which prevents distention of the intestine with gas and fluid and thus tends to prevent leakage and subsequent peritonitis. Our study indicates that ileostomy is an added hazard which increases the operative mortality. Ileostomy was performed in 98 cases. In all of these cases the Witzel method was used. The mortality rate in the 98 cases was 6 per cent higher than it was in the cases in which enterostomy was not performed. Ransom found that the increase in the mortality rate in cases in which ileostomy is performed usually is due to general peritonitis or severe infection at the site of the incision, which often results in a persistent fecal fistula. He concluded that performing an enterostomy is not only unnecessary but unwise. Our findings have led us to the same conclusion.

ONE STAGE RESECTION

In the majority of cases in which resection of the colon has been performed for malignant lesions of the cecum and ascending colon by one of us (C. W. M.), a one stage procedure has been employed and an end-to-side ileotransverse colostomy has been performed.

PROGNOSIS AND FURTHER STATISTICAL ANALYSIS

At present the most satisfactory method of determining prognosis in the individual case of malignant lesion of the colon, rectosigmoid, rectum, and anus is the combined application of Broders' method of grading of malignancy, which is based on the dedifferentiation of cells, and Dukes' (4, 5) classification of such neoplastic growth, which is based on the mural penetration of malignant cells.

Simpson and one of us (C. W. M.), in 1939, reported on the effect of mural penetration of carcinoma cells in the colon. The work was based on an examination of 120 carcinomas of the colon. Dukes' (4, 5) method of classification was modified to fit growths situated above the rectosigmoid and at the same time the growths were classified according to Broders' method of grading. It was concluded that the deeper the carcinomatous penetration, the

TABLE II.—GRADE OF MALIGNANCY

Site of involvement	Cases*	Per cent of cases			
		Grade 1	Grade 2	Grade 3	Grade 4
Cecum	206	14.1	51.5	22.3	12.1
Ascending colon	277	9.4	54.8	25.3	10.5

*Only cases in which grade of malignancy was determined are included.

TABLE III.—GRADE OF MALIGNANCY AND METASTASIS TO LYMPH NODES

Grade	Cases*	Cases with nodal metastasis	
		Number	Per cent
1	55	12	21.8
2	258	75	29.1
3	116	60	51.7
4	54	32	59.3

*Only cases in which grade of malignancy was determined are included

greater was the probability of involvement of lymph nodes and the greater was the probability that the growth would be of a histological grade of malignancy. Likewise, the higher the histological grade of malignancy, the deeper is mural penetration likely to be found, and the more likely it is that lymph nodes will be involved. However, these factors were found to operate independently to a certain degree in that for any class of penetration the prognosis is poorer the higher the histological grade of malignancy; similarly, for any histological grade of malignancy, the deeper the penetration the worse the prognosis. The most precise prognosis is obtained if Dukes' (4) method of classification of mural penetration is combined with Broders' histological grading of malignancy.

Does the situation of the lesion have any influence on the grade of malignancy? If so, what is the status of the cecum and right half of the colon in such a consideration? In both the cecum and the ascending colon one of the most typical features of malignant lesions is the high percentage of tumors which have a low grade of malignancy. While tumors which have a high grade of malignancy do occur and in a percentage greater than in the left portion of the colon, rectosigmoid, rectum, and anus, analysis of the cases in which Broders' scheme of grading was used (Table II) shows that 65.6 per cent of the carcinomas in the cecum and 64.2 per cent of the tumors in the ascending colon were grade 1 or 2. Classification of these tumors by Dukes' system would in all likelihood be of additional value, but an insufficient number of neoplasms in this present series of cases were classified by this method to warrant analysis.

Does the grade (according to Broders' classification) have any influence on the percentage of cases in which metastatic involvement of lymph nodes is present? Metastatic involvement of lymph nodes was noted in 28 per cent of the total number of cases in this series; it was present in 31 per cent of the cases in which the lesion involved the cecum and in 26 per cent of the cases in which the lesion involved the ascending colon. This percentage of metastasis is higher than it is for the rest of the large intestine. In those cases in which the grade of malignancy was determined histologically, there was a progressive increase in the incidence of involvement of lymph nodes as one passes to the higher grades of malignancy (Table III). The lymph nodes were involved in only 22 per cent of the cases in which the lesion was grade 1, whereas they were involved in 59 per cent of the cases in which the lesions were grade 4. This brings out the correlation between the degree of malignancy as it is determined by histological examination and as it is manifested by metastatic involvement. Metastasis to the liver was noted by the surgeon in only 10 per cent of the cases.

It has been noted that when spread of a malignant growth begins through lymphatic channels, the nearest lymph nodes are usually the first to be involved. Neither such involvement of lymph nodes adjacent to the tumor nor even involvement of lymph nodes deep in the mesentery of the right colon should preclude resection of the malignant lesion.

In a recent review of the lymphatic distribution of the colon and rectum, Looney stated that there are comparatively few lymph nodes along the ascending colon and those that are present lie along the medial margin. The lymphatic vessels of the appendix, cecum, ascending colon, hepatic flexure, and the right

TABLE IV.—SURVIVAL RATES IN CASES IN WHICH OPERATION WAS PERFORMED WITH A VIEW TO CURE

Period after leaving hospital	Patients who survived operation*		Survived beyond indicated period	
	Total	Traced	Number	Per cent of traced patients
5 years	302	298	170	57.0
10 years	225	219	104	47.5
15 years	155	150	56	37.3
20 years	91	88	22	25.0

FIVE YEAR SURVIVAL RATES

	Patients who survived operation*		Lived 5 or more years after leaving hospital	
	Total	Traced	Number	Per cent of traced patients
Cecum	127	125	67	53.6
Ascending colon	175	173	103	59.5
Total	302	298	170	57.0

*Inquiry as of January 1, 1939. The 5 year group comprises the patients operated on 5 years or more prior to the time of inquiry, that is, 1933 or earlier; the 10 year group comprises those operated on in 1928 or earlier, and so forth.

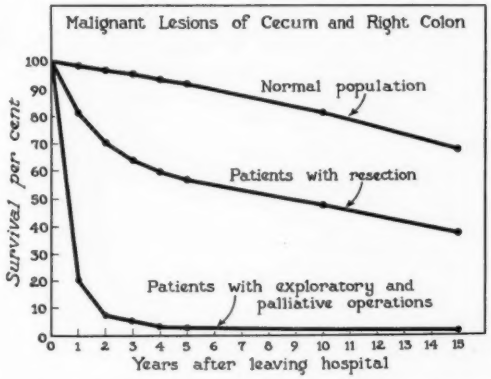

Malignant Lesions of Cecum and Right Colon
Survival per cent
Normal population
Patients with resection
Patients with exploratory and palliative operations
Years after leaving hospital

Fig. 1. Survival rate in cases in which resection was performed with a view to cure.

two-thirds of the transverse colon follow, in general, the distribution of the superior mesenteric artery and end in the superior mesenteric lymph nodes whence the lymph passes through the gastro-intestinal trunk to the cisterna chyli. Raiford stated that the lymph supply to the cecum and right half of the colon is not abundant because this portion of the bowel is primarily concerned with the absorption of fluid. Despite these facts, it has been the observation of one of us (C. W. M.) that the lymph nodes of the right portion of the colon are efficient in maintaining within themselves metastatic deposits for a long period without permitting more distant spread.

SURVIVAL RATES

A word is in order about the way in which the calculation of survival rates was made. For each survival rate, the patients who were operated on the requisite number of years prior to the time of inquiry (which was as of January 1, 1939) were first selected. That is, for the 5 year survival rate the patients operated on in 1933 or earlier were selected; for the 10 year rate, those operated on in 1928 or earlier were selected and so forth. Obviously, therefore, the 5 year rate was calculated on the basis of a larger number of patients than the 10 year rate; the 10 year rate on a larger number of patients than the 15 year rate. Only the patients traced for the requisite number of years were included in the calculation. For instance, of the patients operated on 10 or more years before the date of inquiry, that is, in 1928, or earlier, only those who were traced for 10 or more years were utilized in the calculation of the survival rate. Hence, a patient who had been operated on 10 years prior to the time of inquiry but traced for only 6 years after operation and living at that time was included as traced for the 5 year calculation but was considered untraced for the 10 year calculation.

An exhaustive effort was made to trace all patients. When patients were delinquent in answering the routine follow-up letter, the local health departments, vital statistics bureaus, and so forth, were consulted to learn whether any record of death existed. In the end, only a small fraction of the patients remained untraced. More than 99 per cent of the patients who were operated on 5 years or more before this investigation were traced for 5 years or more.

The survival percentages were calculated on the basis of the patients who withstood the operation successfully; that is, operative mor-

TABLE V.—FIVE YEAR SURVIVAL RATES ACCORDING TO GRADE OF MALIGNANCY—OPERATION PERFORMED WITH VIEW TO CURE

Grade	Total number of patients traced	Per cent of survival
1	31	77.4
2	131	62.6
3	58	51.7
4	26	42.3

tality was not included in the calculation of survival rates. Here, as elsewhere in this study, operative mortality includes all deaths which occurred in the hospital regardless of cause of death or length of time in the hospital after operation.

Table IV presents the survival rates of the patients on whom resection was performed with the purpose of cure, and Figure 1 shows the survival curves for this group compared with that for the patients who underwent palliative operations and with that for the normal population. One of the most striking and encouraging results of this study is the finding of a survival rate, exclusive of hospital mortality, of 57 per cent at the end of 5 years for the group in which resection was performed. It is remarkable that 22 of the 88 patients, or 25 per cent, were alive at the end of 20 years. Further study of the 22 patients who survived 20 years or more shows that 10 patients have survived 25 years or more. On examination of the lesions of these patients, 2 were not graded, 2 were grade 1, 3 were grade 2, 2 were grade 3, and 1 was grade 4. In 1 case in which the lesion was grade 2, the patient is alive 31 years after resection, and in another case in which the grade of malignancy was not determined the patient is alive 30 years after resection.

Comparison of the 5 year survival rates and the site of involvement (Table IV) reveals that 53.6 per cent of the patients were alive at the end of 5 years in the group with lesions in the cecum in contrast to a survival rate of 59.5 per cent when the lesion was situated in the ascending colon. One might hazard the explanation that there is a tendency for the surgeon not to be radical enough in cases in which the neoplasm is limited to the cecum, considering the fact, as has been shown, that in cases in which the lesion is in the cecum the incidence of metastatic involvement of the lymph nodes is higher than in cases in which the lesion involves the ascending colon.

TABLE VI.—FIVE YEAR SURVIVAL RATES ACCORDING TO INVOLVEMENT OF LYMPH NODES AND GRADE OF MALIGNANCY, OPERATION PERFORMED WITH A VIEW TO CURE

Group	Patients who survived operation*		Lived 5 or more years after leaving hospital	
	Total	Traced	Patients	Per cent of traced patients
Nodal involvement Grade 1 and 2	55	55	31	56.4
Grade 3 and 4	45	45	18	40.0
Not graded	25	25	10	40.0
Total	125	125	59	47.2
No nodal involvement Grade 1 and 2	107	107	75	70.1
Grade 3 and 4	40	39	23	59.0
Not graded	30	27	13	48.1
Total	177	173	111	64.2

*See footnote to Table IV.

A study of survival rates in relation to Broders' histological method of grading of neoplasms confirms its prognostic value. The lower the grade of malignancy, the greater are the relative number of patients alive at the end of 5 years. Table V shows how definite is the relationship between the grade of malignancy and the ultimate results. Of 31 traced patients with grade 1 lesions, 77.4 per cent were alive at the end of 5 years, whereas only 42.3 per cent of those whose tumor was grade 4 survived 5 years. It is clear that the grade of malignancy is an outstanding factor in determining results since the survival rate decreases progressively as one passes to the higher grades of malignancy.

The prognostic importance of involvement of the lymph nodes in addition to grade in respect to the 5 year survival rate is shown in Table VI. In cases in which involvement of the lymph nodes was associated with lesions which were grade 1 or 2, 56.4 per cent of the traced patients were alive at the end of 5 years. In cases in which the grade of malig-

nancy was the same but there was no involvement of the lymph nodes, 70.1 per cent of the *traced* patients were alive at the end of 5 years. Of the patients who had grade 3 or 4 lesions which were associated with involvement of the lymph nodes, 40.0 per cent of those who were traced survived for 5 years. In cases in which lesions grade 3 or 4 were not associated with involvement of the lymph nodes, 59.0 per cent of the patients who were traced were alive at the end of 5 years. Regardless of the grade of the malignant lesion, the chances are less in cases in which the lymph nodes are involved than they are in cases in which there is no involvement of the lymph nodes. This table also brings out that, given the fact of the presence or absence of involvement of lymph nodes, the higher the grade of the lesion, the lower will be the number of patients who are alive at the end of 5 years. It should also be noted that although the presence of involvement of the lymph nodes justifies a guarded prognosis, absence of this finding does not necessarily rule out regional extension or metastasis.

SUMMARY

This paper is based on a statistical study of 885 cases of malignant lesions of the cecum and ascending colon, including the hepatic flexure, in which surgical treatment was employed. The study is accumulative for the entire group of these cases which were seen at the Mayo Clinic in the years 1907 to 1938, inclusive. The results presented represent a summation of the work of a considerable number of different surgeons. It must be remembered, therefore, that this presentation is not based on the experience of an individual surgeon nor is it based only on the work as it is done today. For any particular type of operative procedure, whether it be performed in a single stage or in multiple stages, the individual statistics from the standpoint of mortality or morbidity may be better or worse than the general average disclosed by this study.

The main findings are as follows: malignant lesions of the cecum and ascending colon (including the hepatic flexure) constitute 30 per cent of malignant lesions of the abdominal colon, and 12 per cent of malignant lesions of the entire colon including the rectosigmoid, rectum, and anal canal. In 62 per cent of the cases the patients were males and in 38 per cent they were females. In 80 per cent of cases in which the lesion involved the cecum or ascending colon the patients were between 40 and 70 years of age. The average age was 55 years. Anemia is not only an important diagnostic consideration but also definitely increases the operative risk.

Resection with a view to cure was performed in 67 per cent of the cases in this series. This percentage is higher than that reported in cases in which the lesion was found elsewhere in the large intestine. There are many varieties of single stage and multiple stage procedures employed in resection of the cecum and ascending colon. In the interest of the patient, the surgeon should be familiar with all of these procedures. The net hospital mortality rate in all cases and from all causes was 23.5 per cent. Mortality, on the same basis, in cases in which resection was performed with a view to cure, that is, excluding exploration and palliative operations was as follows: for one stage resection, 22.2 per cent; for two stage resection, 28.9 per cent, and for more than two stage resection, 34.5 per cent. This would seem to indicate that, when a one stage resection is found possible and surgically advisable, it has an advantage, in respect to average mortality, over other methods. In 8 per cent of the cases in which a one stage resection was performed, the patients remained in the hospital for more than 35 days, whereas in 78 per cent of the cases in which a two stage procedure was performed, the patients remained in the hospital for 35 days. In cases in which the two stage procedure was employed, 13 per cent of the patients were out of the hospital for 20 to 34 days and another 13 per cent were out for 35 or more days between the two stages. The duration of the malignant lesion in the body appears to have some influence on the 5 year survival rate. In the cases in which the patients were traced the 5 year survival rate was 2.5 per cent greater in cases in which a one stage resection was performed than it was in cases in which a two stage procedure was employed. Enterostomy as an auxiliary surgical measure in any method of

resection of the right portion of the colon appears to be contraindicated as a 6 per cent increase in mortality was found in cases in which this procedure was employed. Survival rates were calculated for various groups in the series. In the group of cases in which resection was performed with a view to cure, the survival rate for 5 years was 57 per cent; for 10 years, 48 per cent; for 15 years, 37 per cent; and for 20 years, 25 per cent.

Grading of neoplasms by the method of Broders has again been shown to be of prognostic value. The survival rate decreases progressively with the higher grades of malignancy. In 65 per cent of the cases the lesion was grade 1 or 2. Involvement of the lymph nodes has been shown to increase directly with the grade of malignancy and to be of prognostic value both independently and in association with the grade of the neoplasm. In cases in which the lesion was grade 1 or 2 and not associated with involvement of the lymph nodes, the 5 year survival rate was 70 per cent. In cases in which the lesion was grade 3 or 4 and associated with lymphatic involvement the 5 year survival rate was 40 per cent. The presence of lymphatic involvement need not be regarded as presenting a hopeless prognosis. In cases in which the lymph nodes were involved, 47.2 per cent of the patients were alive 5 years or more after resection.

REFERENCES

1. Allen, A. W. Right colectomy for malignant disease; a discussion of mortality associated with various operative procedures. J. Am. M. Ass., 1937, 109: 923–928.
2. Allen, A. W., and Welch, C. E. Malignant disease of the colon; factors influencing the operability, morbidity and mortality. Am. J. Surg., 1939, 46: 171–180.
3. Broders, A. C. The grading of carcinoma. Minnesota Med., 1925, 8: 726–730.
4. Dukes, C. E. The classification of cancer of the rectum. J. Path. & Bacteriol., 1932, 35: 323–332.
5. Idem. Examination and classification of tumors of the rectum and of the colon. Am. J. Surg., 1939, 46: 181–185.
6. Harvey, S. C. The one-stage operation for resection of the cecum and proximal colon. New England J. Med., 1934, 211: 1039–1044.
7. Jones, T. E. The treatment of cancer of the colon. Surg., Gynec. & Obst., 1936, 62: 415–419.
8. Lahey, F. H. Neoplasms of the cecum and ascending colon. Am. J. Surg., 1939, 46: 3–11.
9. Looney, W. W. The lymphatic distribution of the colon and of the rectum. Am. J. Surg., 1939, 46: 143–148.
10. Paus, Nikolai. Cancer coli. Acta chirurg. Scand., 1934, 74: 457–462.
11. Pemberton, J. deJ., and Whittaker, L. D. Resection of the right half of the colon. Surg., Gynec. & Obst., 1937, 65: 92–99.
12. Raiford, T. S. Treatment of carcinomas of the large bowel: Part I. The colon. Ann. Surg., 1935, 101: 863–885.
13. Ransom, H. K. Carcinoma of the right colon. Surgery, 1939, 5: 340–357.
14. Simpson, W. C., and Mayo, C. W. The mural penetration of the carcinoma cell in the colon; anatomic and clinical study. Surg., Gynec. & Obst., 1939, 68: 872–877.
15. Stone, H. B., and McLanahan, Samuel. Surgical aspects of carcinoma of the large bowel. J. Am. M. Ass., 1939, 113: 2282–2288.

OMENTAL ADHESIONS SYNDROME

Postoperative Dysfunction of the Transverse Colon

JAMES C. McCANN, A.B., M.D., Ph.D. (Surg.), F.A.C.S., Worcester, Massachusetts

A SENSE of hesitancy is experienced in resurrecting the discussion of the surgical management of postoperative adhesions. Surgical maturity has revealed to the profession, first, that extensive adhesions may cause their carrier but little discomfort; and, second, that lysis of adhesions may further stimulate the process with resultant increased discomfort. However, a 7 years' experience with 23 consecutive cases of symptom producing omental adhesions,[1] has afforded clinical and laboratory data not previously published. These data indicate a distinct clinical syndrome separable from the ill defined category of postoperative adhesions. The syndrome arose from a roentgen demonstrated irritability of the colon based secondarily on omental adhesions, which in turn caused the dysfunction of the colon (Fig. 1).

A careful review of the literature reveals that Howitz (1888–89 and 1893–94), Clark (1904), and Muller (1913) have given careful thought to this lesion. Other less detailed reports (Braquehaye, Craig, Walther, Brown, Hamilton, de Rosas, Gregoire, Pilven, Collins, White and Garside, and Larkin and Burnham) exhaust the list of readily identified contributions relating to this problem.

The omentum is an organ which has excited speculation ever since the ancient Egyptians used it as an augur or "omen" of the hereafter beyond the grave. There have been immense strides in determining its functions from the time when Hippocrates attributed to the omentum the rôle of regulating the fluid content of the abdomen, or Aristotle and Galen attributed to it the rôle of preserving the innate heat of the body, to the present day when its capacity for free mobility and enfoldment of an inflammatory focus have earned for it the sobriquets "fireman," "policeman," and "abdominal leucocyte." The mobility of the organ has been ascribed to gravity (Adami); to intestinal peristalsis (Fisher); to chemotaxis (Hertzler); to extrinsic factors as posture, peristalsis, and diaphragmatic excursions (Florey and Carleton). The mechanism of attachment of the mobilized organ to an irritant has been experimentally investigated by Hertzler, Shutz, and Neuhof and Wiener. They have shown that a general hyperemic engorgement of omental vessels causes the organ to enlarge until one edge contacts and envelops an irritative focus. The rest of the omentum then shrinks to normal dimensions. They also demonstrated that the omentum quickly insinuates itself into peritoneal defects along a suture line. The several histopathological changes which occur in the omentum from its first contact with an irritant to the final stage of firm organization of the adhesions have been exhaustively studied by Ladwig.

CLINICAL OBSERVATIONS

The clinical picture elicited from these cases harboring symptom producing omental adhesions seems to follow a distinct pattern. A brief discussion of one typical case might well introduce the presentation of the composite symptom complex.

CASE 5. White female, aged 45 years, admitted in 1937 with the diagnosis of postoperative omental adhesions, made by Dr. John J. Dumphy. Appendectomy and suspension (etiologic) in 1925 for backache and dysmenorrhea after a fall. An interval right salpingo-oophorectomy and partial lysis of adhesions in 1929 brought slight but transient relief. The patient had always been a perfectly well, active person engaged in nursing duties, prior to the first operation. Her bowels were always regular and she had no gastro-intestinal complaint of any kind. Three years following the first operation she began to be seized suddenly with intense lower abdominal colics which doubled her over and prevented her

[1]Omental adhesions says Haug are noted in 54 per cent of relaparotomies.

Fig. 1. Post-operative omental adhesions. Fixation of the omentum to a low abdominal incision, with right lateral and downward displacement, and fixation under tension of the transverse colon. Fixation under tension is more important in causing dysfunction of the colon than is displacement alone.

from standing erect. She got some relief from bearing down, and from applying heat to her abdomen. This pain was associated with nausea and regurgitation of food into her mouth after every meal. She began to have reflex vomiting of liquids and foods, about 2 months before the current admission. Constipation gradually increased during this whole period, until at the time of admission it had become intractable. Cathartics taken by mouth even in large quantities were of no avail, so that she came to lead an "enema" life. A large part of every morning was spent taking repeated enemas which entailed the greatest suffering because they initiated intense colics. Even with these repeated daily enemas she procured only one movement every 2 or 3 days. A bowel movement caused colic, but subsequently the dejection brought relief. As the constipation increased the colics became unbearable, and as the constipation became less severe the colics subsided somewhat. During the past 2 years this suffering was associated with unnatural intermittent distention of the abdomen with borborygmi, which would develop rapidly and force her to let out her corset strings several inches. By this time she was so incapacitated and invalided that she could not carry on her duties as a nurse. Exertion caused great discomfort, and the effort of walking up and down stairs initiated intense colics. She learned from experience that by limiting the intake of nourishment to liquids during the cyclically recurring spells of colic, distention, obstipation and nausea, she could bring about subsidence of an attack when nothing else would avail. As roentgen studies showed the transverse colon fixed and angulated in the pelvis, operation was advised and accepted. This revealed an omentum adherent in the pelvis and lower abdomen. When the adhesions were released, the medial 8 inch segment of the mobilized transverse colon was seen to form an acutely angulated loop, with the two limbs of the angulated loop adherent to each other over a stretch of 4 inches, from contractures in the gastrocolic omentum. These contractures were severed, and the limbs of the transverse colon separated so as to eliminate the acute angulation. The omentum was resected, and the gastrocolic omentum was reefed. The entire small bowel was absolutely free of adhesions. Exploration of the rest of the abdomen was negative. Postoperative roentgen studies (Fig. 12, Case 5) showed the transverse colon elevated from the pelvis, reduced in diameter, with more normal haustrations. All angulation had disappeared. There was marked axial shortening of the transverse colon, a spontaneous change apparently due to restoration of muscle tone in the released bowel. Following operation there was immediate restoration of spontaneous daily bowel movements for the first time in 10 years. On the tenth day the patient slipped from surveillance to try climbing stairs, and could do it without any discomfort. In 1 year she gained 15 pounds. For 3 years she has been completely free of all symptoms. There is no nausea, vomiting, or colic, and her bowels move daily, with never any need for laxative or enema. The patient has been completely restored to normal health, and does a full day's work regularly.

In grouping the cases for study it is apparent that the initial symptoms appear from a few months to several years following an abdominal operation through a low abdominal incision. The syndrome was never encountered following operations through only a high abdominal incision. The symptoms group themselves into three types: first, reflex symptoms; second, colon symptoms; and third, peritoneal symptoms. The reflex symptoms, developing early or late in the picture, are characterized by epigastric distress after eating, with nausea, regurgitation, and later vomiting. These reflex symptoms occur immediately while eating or within a half hour; also with attacks of colic. They last from a few minutes, to half an hour or more. Vomiting in the later periods may assume such serious proportions that no liquids or foods are tolerated by the patient, with resultant malnutrition, exhaustion, and serious dehydration.

If the reflex disturbance is late in developing, the second group, or colon symptoms—colicky pain, intractable constipation, distention, pain with enemas, painful bowel movements with relief after dejection—appear and dominate the picture. The colon distress consists of intermittent spells of sharp colicky pain, usually in the epigastrium, sometimes in the right or left hypochondrium or lower toward the pelvis. In the absence of extreme fixation of the colon, occasional mild discomfort as from crowding by gas, may announce the bowel involvement. The colicky pain tends to maintain a constant location in each patient, that point depending upon the type of involvement of the colon by adhesions. If there be true angulation of the bowel, as revealed by roentgen study, the colicky pain may be at that point. If the function of the colon is disturbed by tension exerting itself at either the hepatic or splenic flexures, the localization of pain coincides with the area of disturbed physiology—right or left hypochondrium—sometimes with radiation to the back. The location of the pain is predominantly epigastric and right upper quadrant. In the event of failure to procure complete relief by simple lysis of adhesions, the position of the pain may change, depending upon the anatomical relocation of the transverse colon. The onset of the colicky pain is related to eating, defecation, or use of an enema (gastrointestinal activity); also to exertion and abdominal trauma (peritoneal irritation). It comes on arising in the morning, later in the day, or during the night. As time passes it comes more frequently, several times a day, and its intensity augments. Coming in the morning it may be so intense that the patient is unable to move from the bed for half an hour or more, and is forced to lie doubled over, arms around the abdomen, bearing down for relief. There is considerable audible borborygmi during the spells. The patient frequently experiences pain on breathing while enduring these colics.

Constipation varies directly with the intensity of the colic. In the early periods there are less frequent bowel movements with a feeling of incomplete evacuation. As the pain becomes more acute and lasting, the constipation becomes intractable. Massive quantities of cathartics are taken with diminishing effectiveness, and the patient ultimately comes to lead an "enema life." Daily enemas sometimes procure a movement once or twice in several days. The use of an enema or a spontaneous bowel movement may precipitate sudden agonizing colic, although complete dejection subsequently brings relief. There is usually direct correlation between the intensity of the colic and the degree of constipation. As the constipation becomes more marked, the pain is intensified. As the constipation abates, the attacks of pain subside—but only to recur with aggravation of the constipation. In some cases the attacks last for several days, subside, and then recur at intervals of several weeks. In other cases there is constant suffering. In the later periods of severity, the reflex symptoms of nausea and vomiting are aggravated. Vomiting comes once to several times a day and finally occurs whenever liquid or food is taken by mouth. At the height of the crisis of colic and constipation, this constant vomiting produces an extreme loss of nourishment and body fluids. There results an excessive loss of weight with marked dehydration. Rarely is there ever vomiting of upper bowel contents (so called fecal vomiting). A large number of these cases noted that some relief from colic was obtained by going on liquid diet which eliminates the bulky fecal stream. This fact probably accounts for the confusing relief experienced on a liquid Sippy regimen. This fact often leads to the suspicion of an ulcer. One patient attained comfort by maintaining constant watery stools with large daily doses of epsom salts.

Distention is not experienced by all the patients, despite this unmanageable bowel function. The most critical stage of malnutrition, from the vomiting and constipation phases of the syndrome, may be reached without any distention. In most cases, however, distention occurs in varying degrees from intermittent increase of the girth by 2 or 3 inches, to the extreme sudden distention of an acute obstruction. Such an extreme distention is unusual, but may appear overnight. One patient awakened one morning with so marked a distention that a nurse remarked

she "looked nine months along." This distention responds temporarily to medical measures, but only to recur promptly. In mild cases it occurs chiefly after eating. In severe cases, after several days or weeks of distention with associated vomiting and complete obstipation, the distention gradually abates, with progressive subsidence of the other symptoms. Recurring chronic colics then dominate the picture until the next acute seizure develops.

The third group of symptoms (peritoneal) are due to constant tension and intermittent traction on the colon via this fixed omentum, from the pull of physical effort. Some patients become conscious of an intra-abdominal pulling sensation. Colicky pains are stirred up in the colon by the traction that results from exertion. Some patients are caught suddenly with acute discomfort after starting to walk, so that they have to stop on the street and return home. Flexion and extension of the leg or bending the body sometimes initiates pain. One patient had the first sudden seizure of agonizing pain after the unusual exertion of playing twenty-seven holes of golf; another experienced the onset of colic after a severe fall which produced a tearing sensation within the abdomen; still a third patient spent three-fourths of every day in bed to avoid the discomfort caused by the jouncing of an obese abdominal wall; other patients had to give up driving a car because of suffering entailed by the frequent extension of the foot on the pedals; a few patients were awakened from sleep at night by pain initiated from extension of a leg kept flexed to minimize their discomfort. Women stated that they had to give up scrubbing floors because of the intense colic resulting. Kneeling in church acted similarly. The support of a girdle sometimes relieves the downward traction on the omentum, and reduces the discomfort. This peritoneal phase is probably augmented by a low grade inflammatory process and microscopic tears of the omentum, as evidenced by the round cell infiltration and hemorrhagic exudate seen in histological sections. Clinically, this possibility is suggested by occasional fevers (99 to 102 degrees), and leucocytosis (6 cases 11,000 to 15,000).

On physical examination, downward traction of the abdominal wall by the palms of the hands placed over the incision sometimes evokes the characteristic pain. Abdominal tenderness is frequently elicited, and is possibly related to a low grade epiploitis with regional irritation of the involved peritoneum.

When first seen by the physician, these patients present one of three composite clinical pictures. First, and least common, there is an explosive onset of symptoms bearing the features of an acute abdominal emergency. The patient is taken suddenly with unendurable colicky pain, which causes him to cry aloud, and requires repeated injections of morphia for relief. Repetition of the colics, associated with unusual constipation and vomiting lasts for days. All symptoms gradually abate. This type of onset is associated with falls and with unusual exertion. The second group of patients complain characteristically of chronic colics. They give a jumbled story of nausea, vomiting, intermittent distention and constipation with persistently recurring colic, which, until carefully integrated, makes a confusing clinical picture. Acute exacerbations of these chronic symptoms may occur after a fall. Presumably tearing of the fibers of the adherent omentum augments the malfunction of the transverse colon, and the related symptoms. This fact may well account for many baffling seizures of acute upper abdominal pain seen in patients with previous laparotomies, after a serious fall. The third clinical picture characteristic of the advanced stages of the lesion is that of recurring spells of apparent subacute intestinal obstruction. Frequently recurring, intense colics are associated with marked persistent distention, cessation of bowel movements, nausea, and vomiting. This vomiting usually consists in immediate expulsion of slightly altered fluids and foods, shortly after they are ingested. Very rarely there is vomiting of small bowel contents (fecal vomiting), but this suggests concomitant involvement of the small bowel by adhesions. Such obstructive seizures last for several days to weeks, gradually abate, and then are followed by the second type of clinical picture—chronic colic with constipation and occasional vomiting. Roentgen studies reveal

no evident cause for the clinically apparent obstruction. Too frequent recurrence of these critical seizures brings the patient to a state of extreme malnutrition and exhaustion, with death threatened by starvation and dehydration. One patient was observed for 4 years until her death from vomiting, debility, and inanition (Fig. 27).

PATHOLOGY

The postoperative fixation of an omentum to a low abdominal incision is usually a harmless occurrence. In occasional cases, however, an adherent omentum undergoes progressive fibrosis and shortening which produces deleterious results. Fibrosis is initiated at the point of fixation of the omentum and propagates itself in response to the stimulus of trauma, exertion, or infection. This progressive fibrosis replaces the fat and gives a firm consistency to the adherent segment of the omentum. The shirring action of this fibrosis may shrivel this segment to a quarter or a sixth the length of the nonadherent portion of the organ. The extent of involvement of the omentum and colon by adhesions occurs in four degrees: first, adherence of a small area of omentum to the scar; second, adherence of a wide area with definite slight downward displacement of the transverse colon; third, marked contraction of a large fixed segment, pulling the colon deeply into the lower abdomen so as to underly the incision; fourth, extensive surface involvement of the peritoneum with extension of the fibrosing process through the greater omentum up into the gastrocolic omentum, and associated with marked ptosis of the colon. The displacement of the colon is usually proportionate to the degree of involvement of the adherent omentum (Fig. 2).

Histopathological alterations parallel these gross modifications of the omentum. In contrast to the normal omentum (Fig. 3) with its homogeneous network of fat cells containing occasional small bundles of connective tissue, the early stages of this lesion reveal propagating fibrillar processes of connective tissue. These fibrils invade the fatty tissue (Fig. 4), insinuating themselves among the fat cells. The fat cells thus encroached upon become

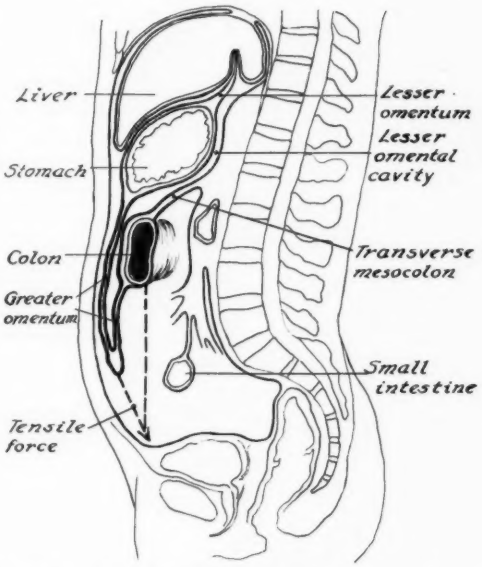


Fig. 2. Mechanism of displacement. Diagrammatic representation of the anatomic relations of transverse colon to the greater omentum, in the layers of which it is incorporated. A tensile force which depresses the greater omentum will simultaneously depress and immobilize the transverse colon. A fixed, progressively fibrosing and contracting omentum will steadily depress the level of the transverse colon, thus subjecting it to increased tension displacement, and fixation.

compressed, reduced in diameter, and sometimes obliterated. Coalescence of these fibrils yields heavy strands of connective tissue which propagate themselves in direct continuity. From these heavy strands, distinct peaked projections of connective tissue spread directly between adjacent fat cells, engulfing, isolating, and obliterating them (Fig. 5). Rarely, the stimulus of repeated operative trauma causes complete replacement of all the fat by a homogeneous sheet of connective tissue (Fig. 6). Detailed histological study reveals an obliteration of fat lobules by proliferating fibroblasts, with engulfment of the irritating end-products of disintegrating fat by numerous giant cells (Fig. 7). Granulating tissue appeared in the partially obliterated lobules of fat ahead of the fibrosing process. Active fibroblasts pervaded all the tissue. Scattered areas of hemorrhage and leucocytic infiltration depicted the influence of trauma.

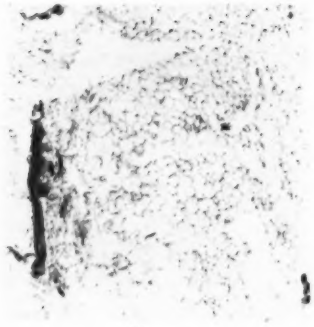


Fig. 3.

Fig. 4.

Fig. 5.

Fig. 6.

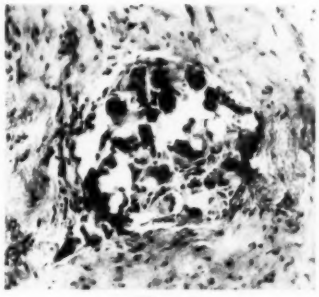


Fig. 7.

Fig. 3. Normal omentum, connective tissue bundle. Fine web-like appearance of sheet of fat cells constituting the normal omentum. At the left of the section note the single discrete bundle of connective tissue. To the right of this is a small zone of collagen or elastic-like fibrillar material. Note the complete absence of invasive characteristics, there being no involvement of adjacent fat cells by extension of this connective tissue component into the normal fat tissue. To the right of the central point of the section are two very small discrete accumulations of lymphocytes and polymorphonuclear leucocytes. ×30.

Fig. 4. Fibrils of connective tissue. Left portion of section is composed of heavy coalesced fibrils of connective tissue which have engulfed many individual fat cells, obliterating them in the areas of heaviest collagen deposit. From this heavy deposit finer fibrils insinuate themselves to the right among the individual fat cells, gradually fading away between the normal fat cells in the right part of the section. Note the smaller compressed appearance of the fat cells in the central portion of the section. At the upper and lower borders of the section is evidence of hemorrhage, to which this process of organization may be related, and which indicates tears from physical exertion and falls. ×30.

Fig. 5. Strands of connective tissue. Heavy strands of connective tissue are directly invading and obliterating the lobules of fat. From the edges of these strands peaked projections of connective tissue extend directly between adjacent fat cells. Discrete fat cells appear engulfed along the border of the strands. This is evidence of direct extension in continuity of this connective tissue strand, independently of propagation by fine fibrils as seen in the preceding section. ×30.

Fig. 6. Sheet of connective tissue. Complete replacement of fat lobules by a continuous sheet of connective tissue. In the upper portion of the section are three completely surrounded lobules, slowly undergoing disintegration from invasion and compression by the sheet of connective tissue. To the extreme right is seen the terminal stage of obliteration, with accumulation of giant cells. ×30.

Fig. 7. Giant cell obliteration of fat lobule. High power study of fat lobule mentioned in the preceding section. Disintegrating fat establishes a foreign body irritative reaction, which calls forth this giant cell reaction. In the same area are large numbers of eosinophiles and young active fibroblasts, evidence of simultaneous destruction of fat, and up-building of connective tissue elements. ×125.

This fibrotic shirring of the fixed omentum caused yielding and downward displacement of the incorporated portion of the transverse colon, with its ultimate fixation. At exploration, whereas the left transverse colon and omentum hung freely in the upper abdomen, the right transverse colon passed sharply downward across the abdomen toward the right lower quadrant. Here the colon was fixed, not directly itself, but indirectly by fix-

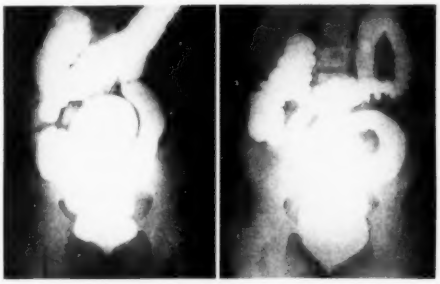


Fig. 8. Case 1. Left, pre-operative; right, postoperative views. Roentgenogram before operation showed dilatation, loss of haustrations, and single fixed loop of transverse colon; postoperative roentgenogram showed bowel with smaller lumen, normal haustra, and U-shaped loop of colon. Patient was a female, aged 26 years who had had an appendectomy at 14 years. Immediately she had spells of colic requiring morphia. Dejection occurred every 7 days. Intermittent distention became the size of 9 months' pregnancy. Vomiting occurred several times daily. She was awakened at night by colics. At operation fecal impaction was noted proximal to fixed loop. The adherent omentum was released. Complete relief of symptoms followed the operation and she since had daily bowel movements.

Fig. 9. Case 2. Left, pre-operative; right, postoperative views. The pre-operative roentgenogram showed a dilated, elongated transverse colon, with double-angled loop. The postoperative film showed smaller lumen, spontaneously shortened transverse colon, and single loop. Patient was a female, aged 31 years, who had had a left adnexectomy at 22. After 8 months she had spells of colic, distention, and vomiting. Intense pains were induced with enemas or movements. She had an 11 weeks' spell of extreme distention, persistent vomiting, and obstipation. Walking or stretching leg caused colic. She lost 60 pounds. At operation the adherent omentum was released and upfolded. Spasm of bowel was visible. Result: 75 per cent improved although there was some persistent vomiting but no colic or distention. Bowels were regular. She gained 15 pounds.

ation of its overlying omentum. It was "frozen" to the abdominal wall under the incision. This carried the right segment of the transverse colon into close proximity to the cecum and ascending colon, to which it occasionally was directly adherent. In 3 cases, 15 per cent, the displacement of the colon was to the left.

Additional direct observations of distortion and dysfunction of the transverse colon were made at the operating table. In 3 cases taut

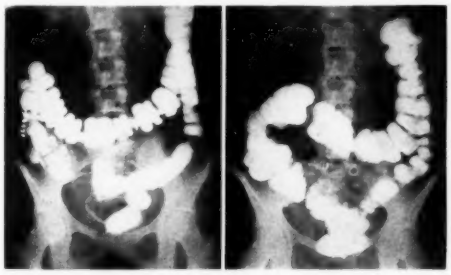


Fig. 10. Case 3. Left, pre-operative; right, postoperative views. Pre-operative roentgenogram disclosed active contractions; angulated hepatic flexure; colon depressed to cecum; postoperative view showed less active contractions, arching hepatic flexure, elevated transverse colon (spontaneous). Patient was a female, aged 29 years. She had had an appendectomy with drainage at 17. Eleven years later onset of "dry heaves" on physical exertion, with frequent colics, severe retching and vomiting, defecation every 7 days, intermittent distention. Scrubbing floors started colic. At operation adherent omentum released, hysterectomy for pelvic inflammation. Immediate relief. Bowels move daily.

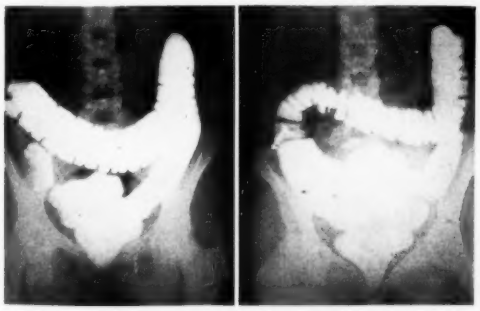


Fig. 11. Case 4. Left, pre-operative; right, postoperative. The pre-operative roentgenogram showed a dilatation, diminished haustra, colon depressed in pelvis; curved left segment. The postoperative film showed a reduced lumen, more normal haustra; colon elevated (spontaneously), angled left segment. Patient was a female, aged 19 years. Appendectomy was performed when she was 16. She had immediate right lower abdominal colics. Eating or rising from bed doubled her over with pain. She stopped eating much because of pain. She was not constipated (1 of 2 cases) but occasional diarrhea. At operation the adherent omentum was released and upfolded. She was relieved of all symptoms and the bowels became regular.

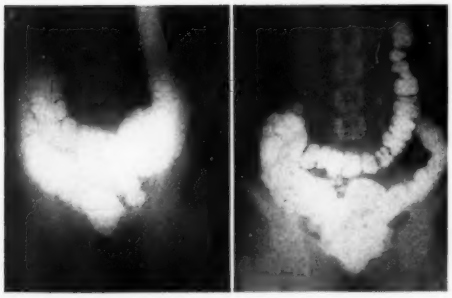


Fig. 12. Case 5. Left, pre-operative; right, postoperative films. The pre-operative film showed an elongated, dilated colon fixed in the pelvis with sharp angulation. The post-operative film showed a spontaneously shortened colon with smaller lumen, elevated from pelvis and with no angulation. This case is reported here in detail. This was one of few instances in which the gastrocolic omentum was reefed. She had complete relief of all symptoms.

Fig. 13. Case 6. Left, pre-operative; right, postoperative films. In the pre-operative film is seen an oblique line to transverse colon, from hepatic flexure to left lower abdomen, colon is elongated and splenic flexure is lower than hepatic. In the postoperative film is shown a horizontal passage (spontaneous shift) of transverse colon from hepatic to splenic flexure, shortened colon (spontaneous), splenic flexure now the higher. Patient was a female, aged 34 years who had had an appendectomy at 18. She had mild symptoms of crowding from gas, distention, constipation. Enema caused intense colics. At operation a small tongue of fixed omentum was found to displace the colon, but not to fix it firmly. This accounted for the mild symptoms. Operation gave relief. She also had a hysterectomy for small fibroids.

bands of fibrosed omentum passed from the involved segment of the transverse colon to the low incision under sufficient tension to angulate it. In 2 of these the proximal segment of colon was grossly distended with gas, and the distal segment was collapsed. In the third case there was a large obstructing fecal impaction proximal to the angulating band. Another case showed an extreme, abnormal looping of the colon with fixation of the loop to ascending colon. Another revealed a gross angulation in the middle of transverse colon where the adhesions pulled it deeply into the pelvis. Two showed transient, firm, localized spasm in mobilized segment of transverse colon after operative release of the adhesions, a condition foreign to the normal colon.

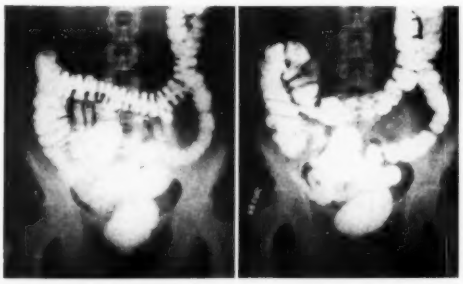


Fig. 14. Case 7. Left, pre-operative; right, postoperative films. The pre-operative view shows a flattened transverse colon, distortion of the hepatic flexure, and excessive hyperperistalsis. The postoperative view shows a curved looping colon; arching hepatic flexure; normal haustra. Patient was a female aged 55 years. Appendectomy was done when she was 31. She was admitted with a diagnosis of bowel tumor. One year after first operation she suffered sharp colics and constipation. She had bimonthly spells of colic, bloating, obstipation, vomiting, and was confined to bed. Walking caused colic. Operation consisting of release and resection of adherent omentum gave complete relief of symptoms and bowels move daily.

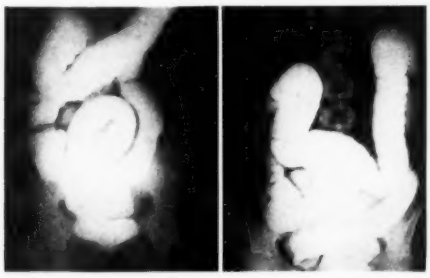


Fig. 15. Left, Case 1; right, Case 2. Physiologic evidence, No. 1—dilatation of bowel; elongation; diminished haustrations. In Case 1 there was the widely dilated lumen of bowel, coincident with obstruction-like episode. There was an apparent functional disturbance of a similar nature in all segments of the bowel. Roentgen report said it suggested obstruction but it was called "colitis." In Case 2 there was extreme dilatation of all portions of colon, particularly of transverse colon, with complete disappearance of haustrations. This roentgenogram taken during an obstruction-like episode, had a roentgen report of obstruction of unknown origin, because the lumen of the bowel was patent.

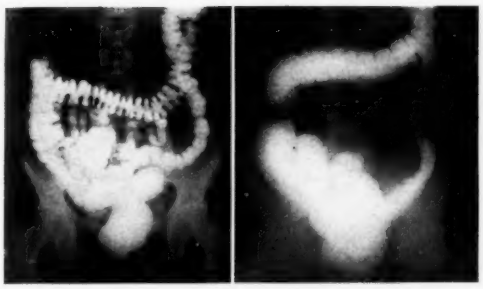


Fig. 16. Physiologic evidence: No. 2—hyperperistalsis —Case 7; No. 3—segmental spasm—Case 14. In Case 7, left, we note excessive contractures of the colon with appearance of an abnormal number of deep haustrations. The overactive state is most apparent in the transverse colon although the appearance of hyperactivity carries over into the other segments. The descending colon is spastic. In Case 14, right, we note spasm in entire segment of descending colon, unaccompanied by any evidence of hyperactivity in other segments of the colon. The overspread of dysfunction into other portions of the colon than the transverse colon is suggested by this study. Spasm disappeared after surgical release of omental adhesions, and the clinical symptoms were relieved.

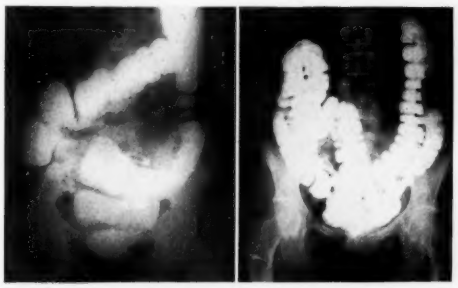


Fig. 17. Physiologic evidence, No. 4—focal spasm. In Case 22, left, we note spastic area at point of fixation of the right portion of the transverse colon by omental adhesions. This observation was made during an operation for another condition, and the roentgenogram was then taken after operation on a positively proved lesion. The roentgenogram at right, Case 2, was taken after an effort to expel the barium clysma. This resulted in a drop of the unfixed left portion of the transverse colon into the lower abdomen, with persistent fixation of the elevated right portion. At the juncture of these two segments is a spastic area which also was visualized at the operating table, when the adherent bowel was released.

PATHOLOGICAL PHYSIOLOGY

Complete pre-operative and postoperative roentgen studies made in 20 of the cases yielded evidence of dysfunction of the colon in 14 of them, 70 per cent. Eight criteria of dysfunction noted may be grouped under two major subdivisions—the physiological and the anatomical evidences of dysfunction.

A. Physiological evidence. (1) Dilatation, diminished haustrations, and elongation of the transverse colon, sometimes interpreted as "colitis" and obstruction, were noted in 8 cases. (2) Hyperperistalsis occurred in 2 cases. (3) Segmental spasm was seen in 2. (4) Focal spasm occurred in 5. (5) Delayed emptying was evidenced in 5 cases by the markedly increased capacity of the colon to empty a

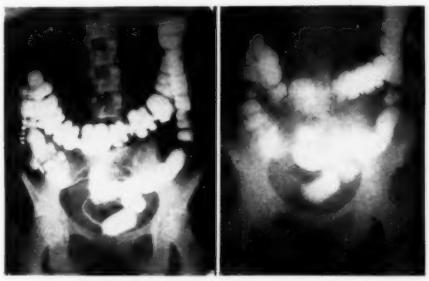


Fig. 18. Physiologic evidence, No. 4—focal spasm. Case 3. Left, pre-operative postero-anterior roentgenogram taken in horizontal position without traction, showing absence of spastic areas which appear in the film at right with traction. In 6 films taken before operation without traction and after operation with traction, there was always absence of spasm. Right, areas of spasm in transverse colon due to traction from omental adhesions when patient is put in Trendelenburg position. This may indicate the mechanism of production of pain upon exertion, whereby the fixed omentum pulls and irritates the bowel.

Fig. 19. Case 6. Pre-operative, left, and, right, postoperative films showing physiologic evidence, No. 5—delayed emptying, (a) barium enema. High grade retention of barium enema in the pre-operative roentgenogram, as compared with the efficient emptying seen in the postoperative roentgenogram, after lysis of omental adhesions. Note different placement, after operation, of transverse colon, which is a spontaneous shift following lysis of adhesions. There were only mild clinical symptoms in this case, even with marked displacement, because of the very limited fixation of the colon.

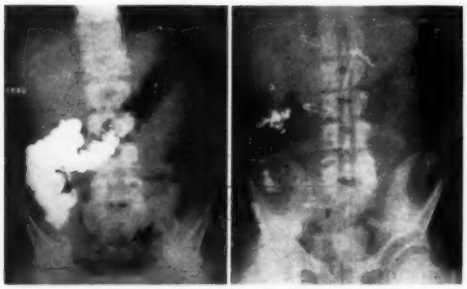
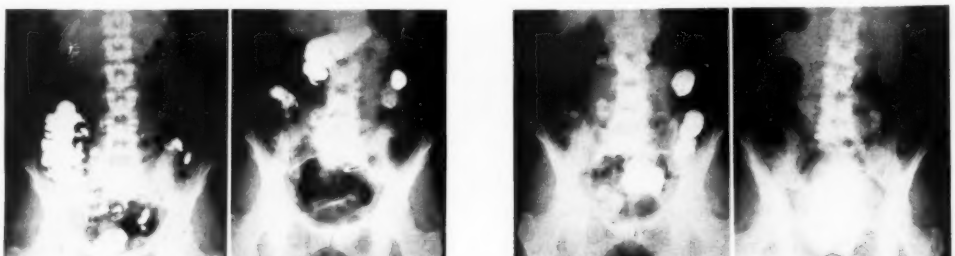


Fig. 20. Case 11. Pre-operative, left, and, right, post-operative films showing physiologic evidence, No. 5—delayed emptying, (b) motor meal. Forty-eight hour retention of barium in right half of colon. This plate taken at 24 hours, duplicates exactly the fluoroscopic finding at 48 hours. Note excess gas in bowel. Quick emptying of motor meal following release of omental adhesions. Part of barium passed by rectum in 12 hours. This 24 hour plate shows nearly complete clearance of all barium from bowel. Note absence of gas.

clysma following release of the adhesions; 3 patients showed extreme delay in the transit of a barium meal from the cecum to the rectum, up to 96 hours; late retrograde transport of barium in the colon many hours after ingestion indicated that this delay may be due to reverse peristaltic waves.

B. Anatomical evidence. Abnormal anatomical conditions were noted from which a consequent dysfunction may be fairly inferred. (6) Angulation, sufficient to impede emptying was noted twice. (7) Loop formation, of an extreme degree was observed once. (8) Fixation of the right transverse colon as noted under the fluoroscope in 8 cases, 40 per cent, was verified by 3 methods: (a) pressure displacement, by which compression and lateral displacement of the abdominal wall carried the fixed colon laterally with it; (b) segmental fixation, by which the right transverse colon remained fixed, while changes in position caused a shift in the position of the free left transverse colon; (c) traction displacement, by which traction on the incision by adhesive strips fixed over the incision, caused measurable shifts in the position of the fixed portion of the colon. Roentgen and operative observations never showed displacement of the stomach.

Correlation of these clinical and roentgen observations with known facts of gastro-intestinal physiology convincingly establish this syndrome. The normal caudad transport of aliment is regulated, as shown by Alvarez, through gradients of activity in the bowel. There is a heightened intensity of rhythmicity, tone, and irritability in the upper bowel as contrasted with the lower bowel. This insures transport of chyme downward, in the same way as the head of pressure at the spigot drives water through a hose to its nozzle. Also important in regulating gastro-intestinal activity is the gastrocolic (ileogastric) reflex described by Macewen (1904), and restudied by Hurst (1913). A neural interrelationship is established by this extrinsic nerve reflex between the stomach and the ileocecal region. By it the activities of these widely separated segments profoundly influence each other; i.e., the intake of food increases the rate of discharge of ileal contents into the colon; and, conversely, irritability in the ileocecal region



a b c d

Fig. 21. Case 18. Physiologic evidence, No. 5—delayed emptying, (b) motor meal. Extreme delay in passage of barium through the colon due to dysfunction from omental adhesions. a, 24 hour progress, most of meal in cecum. b, 48 hour progress, meal delayed in transverse colon c, 72 hour progress, meal has reached descending colon Note excess of gas in proximal colon. d, 96 hour, at which time the meal has finally reached the rectum.

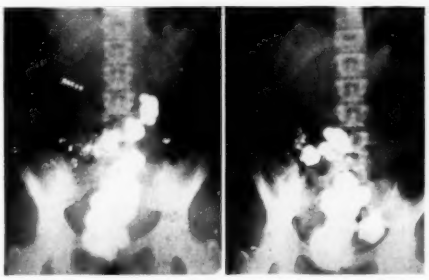


Fig. 22. Physiologic evidence: No. 5—delayed emptying, (c) late retrograde transport (barium by mouth). Case 19. Left, at 48 hours three globules of barium have entered the distal left half of the transverse colon, with part of the mass overlying, and part to the left of the spine. Right, at 72 hours these same masses have been carried backwards to the right of the spine where they have been brought up against the angled portion of the fixed right portion of the transverse colon. This case at 120 hours showed reflux of barium back into the cecum. Note excess of gas.

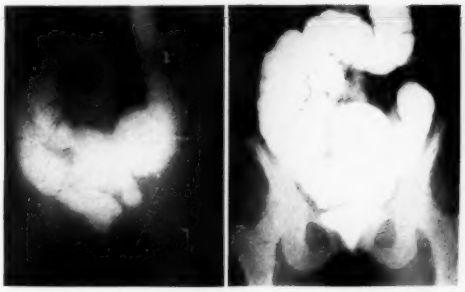


Fig. 23. Anatomic evidence: No. 6—angulation—Case 5; No. 7—loop formation—Case 18. Left, Case 5 shows two arms of the transverse colon descending deeply into the pelvis so as to form an acutely angulated loop, fixed deeply in the pelvis. At the operating table the two arms were adherent to each other with their apex showing such an abrupt turn as to create an obstructing angulation. Right, Case 18 shows an excessively redundant loop of a tremendously dilated transverse colon. The midportion of the transverse colon approximates the hepatic flexure and forms a loop down the full length of the ascending colon and up to the hepatic flexure. The arms of the loop were adherent to each other and to the ascending colon by pathologic postoperative omental adhesions.

disturbs gastric motility, causing nausea and vomiting. Disorders in the functioning of the tract arise from disturbances of these two factors. First, a reversal of the gradients of activity by an irritant causes waves of reverse peristalsis which pass cephalad to the stomach and terminate in nausea and vomiting; second, abnormal stimulation of the gastrocolic reflex by an irritant in the ileocecal region produce irregularities in gastric function which are made manifest by nausea and vomiting—the most dramatic evidence of low bowel dysfunction.

Integration of these clinical, roentgen, and physiological data explains the dysfunction

Fig. 24. Anatomic evidence: No. 8—fixation of colon, (a) pressure displacement. Left, anteroposterior exposure showing fixed right loop of transverse colon close to midline, and only slightly encroaching on the ascending colon. Left half of transverse colon well over to the left, overlying the descending colon. No evidence of hyperperistalsis. Right, postero-anterior position, showing marked displacement of right loop of transverse colon to outer-border of ascending colon, from pressure displacement, with the abdominal wall. Also left portion is drawn away from descending colon. Hyperperistalsis, presumably from traction of the omentum, has appeared in the right portion of the transverse colon.

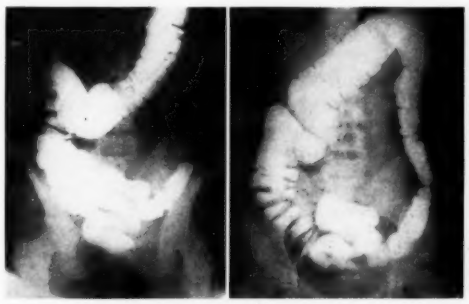


Fig. 25. Anatomic evidence: No. 8—fixation of colon, (b) segmental fixation—Case 23. Left, supine position. There is a normal curvature in the outline of the transverse colon. This routine posteroanterior roentgenogram gives no suggestion of a fixation of the transverse colon. Right, Trendelenburg position. When the position is altered so that the head is down, the free left portion of the transverse colon is thrown into the upper abdomen. At the same time the right portion is held fixed and angulated by omental adhesions. Case 2 (physiologic evidence, No. 4) shows a similar fixation of the right half of the transverse colon when the left half dropped into the pelvis on evacuating the clysma.

Fig. 26. Anatomic evidence: No. 8—fixation of colon, (c) traction displacement. Left, traction upward on adhesive fixed over the incision. Hepatic flexure near the top of the second lumbar vertebra lateral to it. Loop of right transverse colon at level of the lower border of the fourth lumbar vertebra, on a line with the iliac crests. Right, traction downward. By way of contrast hepatic flexure has dropped to the top of the third lumbar vertebra overlying it. The loop of right transverse colon is down to level of the lower portion of the fifth lumbar vertebra, far below the level of a line across the iliac crests.

a b c

Fig. 27. Case 20. a, In 1935, patient's weight was 250 pounds. Hysterectomy 2 years before in 1933. Perfectly well; working, no pain, bowels regular. b, In 1937, she weighed 175 pounds. For 1 year spells of colic, vomiting, and progressive constipation, with intermittent distention. Beginning obstruction-like episodes. c, In 1939, her weight was 125 pounds. Repeated hospitalization for obstruction-like episodes, with reflex vomiting. Total incapacity from colic, vomiting, constipation. Operated upon for omental adhesions. No other disease demonstrable after repeated roentgen studies and 3 laparotomies. Patient died in May, 1940, 4 years after onset of the syndrome, from inanition, exhaustion, and terminal pneumonia.

arising from omental adhesions. The irritating effect of omental adhesions on the colon has been noted clinically and by roentgen study. Clinically, the pull of the adhesions from exercise, stretching, extending the leg, driving an automobile, kneeling, washing the floor, walking, established a degree of irritability which announced itself locally by colic, and reflexly by nausea and vomiting; serious falls, producing a tearing sensation in the region of the adhesions, were followed by prolonged intense colics. Roentgenograms taken when traction was purposely produced on the colon via the omentum showed spasm which was not present in the absence of traction; 30 per cent of the pre-operative roentgenograms showed dilatation and diminished haustrations, called "colitis"; 20 per cent showed a toneless elongation of the transverse colon which disappeared following release of the adhesions, apparently from restored tone; 30 per cent showed heightened irritability as manifested by local or segmental spasm or general hyperperistalsis; 25 per cent showed evidence of delayed emptying of the colon; 15 per cent showed late retrograde transport of barium. Gross visual evidences of dysfunction noted at the operating table were: excessive distention by gas of the segment of colon proximal to the adhesions; impaction of fecal matter proximal to the fixed angle of the bowel; transient marked spasm in the released segment of colon. From this demonstrated irritability in the colon arose the clinical manifestations of dysfunction—intractable constipation, chronic colic, distention and borborygmi, reflex nausea and vomiting. This irritability was stimulated by normal functional activities; the intake of food, and the act of arising from bed in the morning, stimulated a discharge of chyme from the ileum into the cecum which caused hyperactive irritability in the adherent bowel, as manifested by intense colics and reflex vomiting; initiation of peristalsis by spontaneous bowel movement or injection of an enema, produced excruciating colic and sometimes vomiting. Thus so accurately do the clinical and roentgen observations integrate with the established facts of gastro-intestinal physiology as to justify presentation of this clinical picture as a specific syndrome having an adequate physiological background.

TREATMENT

Prevention of the lesion is of paramount importance. In operative procedures through low abdominal incisions, particularly in female patients in the early decades of life, all trauma to the omentum and peritoneal edges must be sedulously avoided; the omentum must never be caught in the suture line; a high lying omentum must never be pulled into the lower abdomen during the final peritoneal toilet; the peritoneum is best closed by a running mattress suture which produces ectropion of the rough edges; postural drainage by head blocks is preferable to Fowler's position, which crowds the omentum into the lower abdomen.

The surgical release of the omental adhesions is usually best accomplished through a low incision in close proximity to the adhesions. Occasionally, following multiple operations, or with roentgen evidence of ptosis of the colon requiring a reefing of the gastrocolic omentum, a high incision is preferable. Following release of the adhesions, three procedures proved valuable in preventing recurrence of the lesion; (1) resection of the released, fibrosed segment of omentum; (2) upfolding the omentum and fixing it with sutures to the gastrocolic omentum; (3) reefing the gastrocolic omentum, in the presence of marked ptosis, so as to elevate the bowel from the lower abdomen.

Further radical measures were attempted in 3 cases which suffered recurrence of incapacitating symptoms. Ileosigmoidostomy was first tried but it failed to bring relief because of a roentgen demonstrated reflux of barium back to the cecum past the adherent, irritable bowel. Right colic exclusion (transection of the transverse colon with stoma drainage of right half; left ileo-transverse-colostomy), thus isolating the irritable right colon from the functioning intestinal tract, was then tried. One patient showed no improvement, while 2 were improved about 50 per cent. These few cases do not permit evaluation of this method. Apparently there always will remain a small residuum of victims harboring vicious omental adhesions, to whom neither the internist nor the surgeon can bring lasting relief. During the postoperative period, in addition to routine postoperative care, elevation of the foot of the bed on blocks will carry the released bowel into the upper abdomen away from the peritoneal tags from the released omentum. Amfetin was sometimes used.

ANALYSIS OF STUDY

The preponderant incidence of this disease among women is striking. Wherever noted, the sex of all cases reported in the literature was female. In this series, whereas 20 women, 85 per cent, were operated on, only 3 men, 15 per cent, were encountered. After excluding 6 pelvic operations, there was an etiological incidence of 14 appendectomy incisions among women as against 3 appendectomy incisions among the men. Except in terms of a constitutional sex factor, this extreme discrepancy between the sexes in the ratio of 4:1 is not easily explainable. Possibly the higher incidence of a ptotic habitus and low lying colon and omentum among women has some bearing on this anomaly.

Analysis of the age relationships is instructive. The primary operation which caused the adhesions was performed at an age under 20 years in 12 cases; during the twenties in 7 cases; during the thirties in 3 cases; after 50 years in 1 case; excluding the last case the average age at the time of the primary operation was 20 years, making the lesion a surgical hazard of youth. The time interval between the primary operation and the onset of symptoms ranged from a few months to 19 years, averaging 3½ years. The duration of suffering between the onset of symptoms and the current lysis of adhesions ranged from 2 to 18 years, averaging 8 years. The current operation was performed at an average age of 33 years, the youngest patient being 17 years of age, and the oldest 67. Interval operations had been performed with no relief in 12 patients, 50 per cent of the group, with the sacrifice of many innocent organs, chiefly the gall bladder and pelvic organs; 5 patients had 1 interval operation; 2 had 2 operations; 2 had 3 operations; 2 had 4 operations; 1 had 6 operations—a grand tally of 29 unsuccessful interval operations.

The etiological significance of infection as compared with aseptic trauma, in causing these adhesions, does not appear as impressive in this series, as it did in the study by Muller

and Rademaker. In 16 of the present cases characterized by but one or two operations before the current lysis of adhesions, all hospital records were available for study. Analysis of the factors of operative trauma and infection grouped these cases naturally into 3 divisions. In the first subgroup there were 10 patients who were subjected to clean surgical procedures; there was no infection at the time of operation; the peritoneum was closed without drainage; the postoperative course was uneventful, with no unusual febrile reaction; the patients were discharged early with cleanly healed incisions. Only the factor of aseptic trauma may be fairly incriminated in these cases. In the second group there were 3 cases in which operation was done for acute appendicitis. There was no recorded infection of the peritoneal cavity at the time of operation, and drainage was not instituted; the incision healed cleanly by first intention; the patients were discharged early. Although infection may have played a minor rôle in this group, certainly operative trauma appears to have been the major factor in causing these adhesions. The third group, presenting frank records of acute suppurative appendicitis with peritonitis, for which drainage was carried out, contained only 3 cases. Infection in this group was probably the dominant factor in causing adhesions. In summary, an evaluation of the factor of aseptic operative trauma versus infection as the causative agent of symptom producing omental adhesions, indicates, that in 60 per cent of the cases, the adhesions resulted from aseptic operative trauma; that in 23 per cent they were due to aseptic trauma predominantly, with a minor element of infection; and that in only 17 per cent was the formation of adhesions due primarily to infection.

Diagnosis may be difficult if all the components of the syndrome are not present. In this series, the reflex symptoms, sometimes appearing late, were elicited from all but one patient; the elements of the colon complex were always present in part or entirely; peritoneal symptoms were noted in 13 instances, denied in 3, and not recorded in 7. In the present series a pre-operative diagnosis was achieved in 17 of the 23 cases, 74 per cent, frequently by other physicians acquainted with this study. In differential diagnosis this lesion is widely disregarded. It is confused with gall-bladder, ulcer, and pelvic diseases, and postoperative hernia. The most difficult differentiation is between omental adhesions and small bowel adhesions. The cyclical recurrence of obstruction-like episodes characterized by the early reflex vomiting of stomach ingesta, usually with spontaneous subsidence of the condition, is the chief distinguishing characteristic of omental adhesions. "Effort" or "traction" colic, as well as the predominant "colon" features in the story, balance the differentiation more toward omental adhesions. "Fecal" vomiting instead of "reflex" vomiting almost commits the diagnosis to small bowel adhesions. Doubtlessly, many clinical reports of satisfactory conservative management of intestinal obstruction include cases experiencing the cyclical exacerbation of symptoms from omental adhesions, unrecognized in the absence of surgical exploration; also it is quite possible that poor results following an apparently satisfactory technical management of small bowel adhesions, may represent persisting symptoms from coexisting omental adhesions, not evaluated or corrected at the time of operation. The chief offense is labelling these sufferers "psychoneurotics" as was done in 14 of the cases. Probably many functional diagnoses of atonic or spastic constipation, colitis, irritable colon, functional indigestion—all fortified by negative roentgen reports—represent inadequate evaluation of the secondary functional manifestations of omental adhesions.

The results of operative intervention—granting 25 per cent each for the four major complaints, such as colic, constipation, distention, and vomiting—show in the final summary of 20 completed cases: 12 patients, 60 per cent, completely relieved; 2 patients, 10 per cent, 75 per cent improved; 4 patients, 20 per cent, 50 per cent improved; 2 patients, 10 per cent, entirely unrelieved. One patient died from unexplained intestinal obstruction unrelieved by ileostomy. Another patient was followed for 4 years to the final outcome of death from recurring spells of vomiting, from debility and inanition. The surgical failures

among these "omental cripples" are a source of oppressing concern to the surgeon who must watch their hapless invalidism.

CONCLUSION

A surgical experience with 23 cases of symptom producing omental adhesions, unrelieved by medical care, has yielded clinical, pathological, and roentgen data not previously published in the literature. These data appear to justify this presentation of a specific syndrome based on a dysfunction of the transverse colon, induced by pathologically fibrosed, adherent omenta, fixed under tension to a low abdominal incision.

I wish to express my indebtedness to Dr. Andrew E. O'Connell for his patience in carrying out repeated roentgen studies in this unpromising group of patients.

BIBLIOGRAPHY

1. ADAMI. The great omentum; Phila. M. J., 1898.
2. ALVAREZ, W. The Mechanics of the Digestive Tract. New York: Paul B. Hoeber, Inc., 1928.
3. BRAQUEHAYE, J. Bull. de l'hôp. civ. franç. de Tunis, 1900, III: 204–248.
4. BROWN, LER. Am. J. Obst., 1912, 65: 480.
5. CLARK, J. G. Surg., Gynec. & Obst., 1909, 9: 603–607.
6. COLLINS, F. K. Calif. & West. Med., 1929, 28: 179–182.
7. CRAIG, D. H. Am. Med., 1903, 6: 438.
8. FISHER. Brit. M. J., 1906, 1: 235.
9. FLOREY, H., and CARLETON, H. M. J. Path. & Bacteriol., 1926, 29: 97–106.
10. GOMEZ DE ROSAS N. Rev. méd. cubana, Habana, 1924, 35: 204–207.
11. GREGOIRE. Quoted by Pilven.
12. HAMILTON. Australas. M. Gaz., Sydney, 1913, 33: 619.
13. HAUG. Muenchen. med. Wchnschr., 1923, 70: 463.
14. HERTZLER, A. E. J. Am. M. Ass., 1913, 60: 1292.
15. Idem. Tr. West. Surg. Ass., 1916, 26: 99.
16. Idem. The Peritoneum. Vol. 1, p. 309. St. Louis: C. V. Mosby Co., 1919.
17. HOWITZ, F. Kjøbenh., med. Selsk. Forh., 1888–89, 112.
18. Idem. Kjøbenh., med. Selsk. Forh., 1893–94, 23–24.
19. HURST, A. F. J. Physiol., 1913, 47: 54–56.
20. LARKIN, C. L., and BURNHAM, N. G. New England J. Med., 1940, pp. 208–213.
21. LADWIG, A. Arch. f. klin. Chir., 1928, 1: 151.
22. MACEWEN, W. Lancet, 1904, 2: 995–1000.
23. MORRISSON. Brit. M. J., 1906, 1: 76.
24. MULLER, G. P. Pennsylvania M. J., Athens, 1913–14, 17: 621–625.
25. MULLER, G. P., and RADEMAKER, L. A. Arch. Surg., 1933, 26: 208–287.
26. NEUHOF, H., and WIENER, S. Surg., Gynec. & Obst., 1910, 11: 348–349.
27. PILVEN, M. J. Bull. et mém. Soc. de chir. de Par., 1925, 51: 35–37.
28. SCHUTZ, C. B. Surg., Gynec. & Obst., 1930, 50: 541–544.
29. WALTHER. Bull. et mém. Soc. de chir. de Par., 1905, 31: 396–399.
30. WHITE, P. A., and GARSIDE, A. A. Illinois M. J. 1931, 59: 124–125.

THE INTRA-ABDOMINAL APPLICATION OF SULFANILAMIDE IN ACUTE APPENDICITIS

JAMES E. THOMPSON, M.D., F.A.C.S., JOHN A. BRABSON, M.D., and JOHN M. WALKER, M.D., New York, New York

THIS paper is an analysis of acute appendicitis at the Roosevelt Hospital during the 6 year period of 1935 to 1940, inclusive; the first 5 years represent an average background against which we hope to contrast the results of those cases during 1940 in which patients were treated by the intra-abdominal application of sulfanilamide.

Full credit must be given to the two men responsible for the first use of the drug at our hospital. First to Dr. R. Sterling Mueller who had the courage to sprinkle copious quantities into the peritoneal cavity in what seemed a hopeless case of peritonitis; and second, to Dr. William H. Cassebaum, who leaning over his shoulder at the time of operation, collaborated in the idea. The procedure was taken up immediately by one and then another of our surgical staff, and now is routine when indicated.

To make a thorough analysis of this sort requires a great deal of careful, and frequently tedious, work tabulating facts garnered from histories for later interpretation. The histories of over 1000 cases during the 6 year period were reviewed, in order to include only those cases of definitely acute appendicitis. We then eliminated several hundred borderline cases and others which were definitely not in this strict classification. Those thrown into the discard included cases of acute catarrhal, interval, subsiding acute, chronic, and mechanical varieties; cases of acute mesenteric lymph adenitis; and frequent ones reported by the pathologist as showing either fibrosis or a normal appendix.

Our series thus represents, as accurately as it was possible to determine, the distinct group of acute suppurative appendicitis known in operating room jargon as the "red hot" appendix.

The surgical concept of the signs and symptoms, and the diagnosis of acute appendicitis has changed little in the past three decades, but there have been great advances in the surgical technique. The mortality rate has continued to be sizeable in spite of these improvements, and periodically we are alarmed with reports that it is on the increase. In an effort to lower this rate, every encouragement should be, and is, given to any safe method which will accomplish this end.

The management of this condition at the Roosevelt Hospital has not changed since 1935 except in relationship to the use of sulfanilamide. We consider every case to be an acute surgical emergency, whether it be day or night. We do not believe in the conservative treatment of peritonitis and delay operation only long enough to replenish fluids, electrolytes, or blood proteins where such treatment is believed to be indicated. The occasional patient is seen, however, in such a critical state that even the slightest trauma under local anesthesia would be fatal; here we recommend delay and transfusions. Two such instances occurred during the 1935 to 1939 interval: one patient died within a few hours and the other improved sufficiently to be operated upon at the end of 24 hours, only to succumb later.

A case diagnosed as appendiceal abscess when patient is admitted to hospital is delayed if the operator feels the localizing process has been completed; but when doubt exists, immediate operation is believed to be safest.

The McBurney incision is routinely employed whenever the diagnosis of acute appendicitis is made, and we feel that it has been largely responsible for a nominally low mortality rate. It was used in about 95 per cent of our cases.

From the Surgical Services of the Roosevelt Hospital, New York, N. Y.

Read before the Surgical Section of the New York Academy of Medicine, January 3, 1941.

The appendix is removed by cautery or the phenol knife and inverted with a linen pursestring suture re-enforced by a Lembert of catgut without ligating its base. Simple ligation of the base without inversion of the stump is reserved for those patients with inflammation and resultant thickening of cecal wall, or if application of the pursestring is technically difficult.

In the presence of an appendiceal abscess, when exposure and removal of the appendix increase the possibility of spreading the infection to uninvolved peritoneum, simple incision and drainage are employed with the intention of secondary appendicectomy at a later date. Otherwise the appendix is removed and the wound is closed about one or two drains. The soft rubber fenestrated tube has been the drain of choice, since we believe that the establishment of a tract can be obtained best in this manner.

In the presence of peritonitis the usual procedure is to place a drain down to the pelvis and another to the site of the appendix stump. The peritoneum is rarely closed without drainage.

In the simple acute case the wound is closed in layers without drainage; in cases of doubtful localized peritonitis a soft rubber tube or Penrose drain is placed down to peritoneum and the abdominal wall is closed singly about the emerging drain.

The great majority of patients requiring drainage of the peritoneal cavity have been closed after the manner recommended by Dr. John Garlock, which consists in simple closure of the peritoneum about the drains, with the remainder of the wound left wide open. A few of the surgeons have approximated transverse muscles and internal oblique muscles in addition.

In an analysis of such a series of cases as we are presenting, certain criteria must arbitrarily be chosen to classify the various types of lesions so that they may be easily and clearly understood as well as easily and accurately compared with similar groups. It is for this reason that we eliminate the many confusing terms and classify this series of cases of acute appendicitis as recommended by Dr. Mont R. Reid.

Group 1. The simple acute appendicitis. In this variety there is no gross evidence of perforation; the fluid about the appendix if present is not frankly purulent, and a culture of such fluid if taken has been reported as showing no growth.

Group 2. The acute appendicitis with localized abscess formation.

Group 3. The acute appendicitis with peritonitis. This final group includes both those cases of spreading or diffuse peritonitis and those of the localized variety. It is believed that a true knowledge of the extent of a peritonitis is impossible to obtain through an ordinary incision. The impression would vary with the individual surgeon and could be accurately determined only after a very improper operation (6).

In most instances the operator's vivid description of the peritonitis left no doubt that it belonged in this group, but occasionally his description was doubtful and, in such an instance, dependence was placed on a positive culture. When a culture of peri-appendiceal fluid was reported positive for Bacillus coli or streptococcus, even though no gross perforation was detected and even if the appendicitis had been described as the simple acute variety, we classified it as a case of localized peritonitis. In the cases of abscess formation or peritonitis, we found that Bacillus coli was the causative organism in 83 per cent of cases. Other organisms encountered as etiological factors in their order of frequency were: gamma streptococcus and beta streptococcus. Sometimes associated with Bacillus coli or with the streptococcus organisms were Bacillus proteus, Bacillus lactis aerogenes, and Bacillus mucosus capsulatus. No anaerobic cultures were done.

In January, 1940, we began using sulfanilamide crystals placed directly into the peritoneal cavity as an adjunct in the treatment of acute appendicitis with perforation and peritonitis. The first few patients were desperately sick, the peritonitis in each instance seemed diffuse in character, and the fluid was frankly purulent and had a fecal odor. The convalescence and cure of these patients was so dramatic, that one could not help but be impressed with the value of the drug used thus.

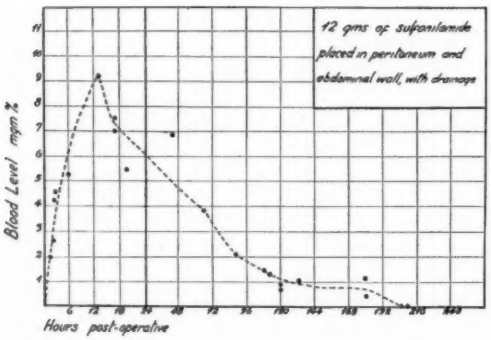


Fig. 1. Computed average blood level curve. This chart includes all patients who received a total of 12 grams of sulfanilamide and on whom postoperative blood levels were taken. The number of levels taken on each patient varied from 1 to 8. None of these patients received sulfanilamide after operation by any route. Each of the points on the graph represents time indicated. From these scattered points a curve was drawn which roughly indicates the rate of absorption of the drug and maintenance of the blood concentration.

The technique employed was at first rather crude, consisting in pouring the crystals directly into the depths of the wound with the retractors spread widely apart and lifted in order to give greater depth to the peritoneal cavity. The drug, sterilized only by the chemical company at the time of preparation, was poured directly from the prontylin bottle into a sterile 1-ounce measuring glass held by a suture nurse. If 2 drams of the drug were used, we knew by rough computation, previously determined by the druggist, that 5.5 grams had been administered.

We later discovered that it could be sterilized without disturbing its crystalline powdery form. The crystals were found difficult to manage the minute they struck moisture, and in this respect greatly resembled sugar. A moist heat used for sterilization that can penetrate to the drug converts it into a hard rock-like mass on drying; for this reason autoclaving is unsatisfactory.

The sulfanilamide is now weighed in the drug room, put into test tubes in 2, 4, 6, and 8 gram quantities, and each tube snugly stoppered with cotton. The tubes are then sterilized by placing in an oven, where the heat is maintained at 120 degrees C, for one-half hour.

The test tube is a handy container, as it has been the most effective implement for depositing the crystals in the peritoneal cavity. An implement, such as a long handled gall-bladder scoop, which allows blood, serum, or peritoneal fluid to touch the drug, immediately converts the soft dry powder into a wet sugary substance that clings to the applicator.

We have placed varying quantities within the peritoneal cavity. A smaller amount is often placed in the abdominal wall layers during closure, as we have found wound healing aided by this maneuver in the frankly purulent cases. There is no doubt that involvement of the wound thus seems much more limited and localized to the vicinity of the emerging drain. This feature has been such a consistent finding that it is a great temptation to discard the Garlock method of closure.

Postoperative sulfanilamide blood levels have been taken at frequent time intervals. The initial rise is prompt and fairly consistent, the fall in blood level is much more gradual, but shows the same consistency (Fig. 1). When the drug is put only in the peritoneal cavity and not in the abdominal wall, the fall is very abrupt. The average peak obtained was 6.9 milligrams of sulfanilamide per 100 cubic centimeters of blood, and the average time at which this point of maximum concentration was reached was 14.7 hours after operation.

The height of the original rise is entirely dependent upon the amount used, and also upon the amount which is lost in the presence of a drain. The length of time in which one can expect to get a positive blood level is also markedly influenced by the presence of drains and is in direct proportion to the amount placed in the muscle and subcutaneous layers.

These findings imply that the drug is absorbed from its local storehouse at a definite rate. The greater the amount used and the less it is allowed to be lost through drainage, the higher the possible blood level. It also indicates that the body absorbs the drug much more rapidly from the peritoneum than it does from the muscle or fat.

Draper and Kauer have shown in dogs that, after intraperitoneal use of sulfanilamide, blood level reached its peak in about 6 hours and rapidly approached zero in 65 to 75 hours.

TABLE I

	Number of cases	
Total cases	59	145
Complication	Sulfanilamide in peritoneum	None used
Wound complication	6*	5
Prolonged temperature	7	0
Pulmonary embolus	2	3
Serum in wound	1	0
Fecal fistula (temporary)	2	0
Upper respiratory infection	1	2
Secondary peritoneal abscess	1	1
Jaundice	1	0
Atelectasis	0	3
Phlebitis	0	1
Hematuria	1	0

*This term does not apply to cases of prolonged wound drainage, but indicates those cases showing secondary wound abscess. We feel that too much dependence was placed on the sulfanilamide in these cases, and improper drainage of the wound was performed.

It is our contention that there is a tremendous concentration of the drug locally, many times the amount represented by its blood level, and that the mode of attack against the peritonitis is much akin to an *in vitro* destruction of the bacteria.[1]

Postoperative blood levels have been taken in a few cases at 2, 4, 6, 12, 18, and 24 hour intervals, and subsequently at 8 o'clock each morning until the report is completely negative for any trace of sulfanilamide. In others, the levels were taken at sporadic intervals. The impression has been gained that the point of maximum absorption into the blood stream occurs at about 12 hours from the time of its introduction and then steadily declines.

The average adult dosage recommended in case of peritonitis is 8 grams intraperitoneally and 4 grams placed in the abdominal wall layers. A few grams more can be used in the treatment of severe diffuse peritonitis, and less in the treatment of the definitely localized variety. The appendiceal abscess seems to lose the drug more rapidly by drainage, and in this type it is safe to use as high as 20 grams total.

Age and weight are factors which modify dosage; in infants and children we have used one-quarter or one-half the amount employed for the adults. It is safe to calculate the dosage on a basis of 175 milligrams per kilogram of body weight.

[1]The Winthrop Chemical Co. Inc., informs us that from 1.57 to 1.60 grams of sulfanilamide will dissolve in 100 cubic centimeters of beef serum at 37 degrees C. This approximates what one might expect to take place within the peritoneal cavity in the human, and would give under these circumstances a concentration of about 1600 milligrams per cent.

TABLE II.—COMPARISON OF IMPORTANT COMPLICATIONS

Type of complication	1935–1939 (741 Cases)		1940 (204 Cases)	
	No.	Percentage of total cases	No.	Percentage of total cases
Wound infection	85	11.5	11	5.4
Secondary peritoneal abscess	21	2.8	2	0.9
Atelectasis	16	2.1	3	1.4
Pneumonitis	12	1.6	0	0
Wound separation	8	1.1	0	0
Phlebitis	5	0.7	1	0.5
Pylephlebitis	2	0.27	0	0
Jaundice	1	.13	1	0.5

One of the patients with abscess had a secondary appendectomy about 2 months later. The lack of adhesions encountered and the normal appearance of the peritoneum were striking. This one example adds to our general impression that the drug does not irritate the peritoneum.

We have noticed no definite toxic effects from the use of the drug administered in this fashion except some cyanosis, which, though not a constant feature, is usually evident. The nausea and vomiting, if present, have not been sufficiently distinguishable from that to be expected in a convalescent from an appendectomy.

There have been no cases of leucopenia or agranulocytosis, but there was 1 case of jaundice which was felt to be secondary to the streptococcus peritonitis, as it disappeared under the continued administration of sulfanilamide by mouth (Table I).

Persistent elevation of temperature did occur in a few instances, and in several of these cases it was felt directly attributable to the sulfanilamide.

In those patients in whom sulfanilamide was used the age varied from 1 to 72 years. The lesion in 45 per cent of the peritonitis group could definitely be considered diffuse. Many of these patients were critically ill, and in a few the constitutional condition of the patient and the local findings presented a

TABLE III
1935–1939

Type	Cases	Deaths	Mortality
Acute	566	3	0.53%
Abscess	59	4	6.78%
Peritonitis	116	13	11.20%
Total	741	20	2.7%

hopeless picture. We feel that the cure in these instances was nothing short of miraculous.

Sulfanilamide was used in a total of 59, or 29 per cent, of the cases, representing each variety of our three groups of the disease. In 14 of these 59 instances it was continued either per rectum or by mouth because of the extremely severe pathological process encountered at operation or the continued critical condition of the patient. The added experience with dosage has led us to believe that a sufficiently large intra-abdominal application eliminates the necessity for any continued postoperative administration.

RESULTS

During the 1935 to 1939 period a total of 741 patients with acute suppurative appendicitis were operated upon, with 20 deaths, a total mortality rate of 2.7 per cent (Table III). A fuller analysis of these deaths can be obtained from glancing at the accompanying table (Table IV), but needless to say the majority were directly attributable to peritonitis. The 3 deaths which occurred in the acute variety give a mortality rate which, although low, has been reported considerably lower for this group by other clinics (Table V). One of these deaths was due to a bad rheumatic heart, one to pylephlebitis and septicemia, and the third to poor surgical judgment, as an inadequate operation had been performed.

TABLE IV.—ANALYSIS OF DEATHS
1935–1939

	Cases
A. Diffuse peritonitis	12
B. Post operative pneumonia	3
C. Pylephlebitis and septicemia	2
D. Pulmonary embolism	1
E. Rheumatic heart and decompensation	1
F. Acute purulent cystitis	1
Total	20

Acute	A+C+E = 3
Abscess	A+B+C+F = 4
Peritonitis	10A+2B+D = 13

The mortality rates for the abscess and peritonitis group are low as compared generally with statistics from other hospitals.

During 1940 we treated a larger total number of patients with appendicitis than had ever been treated in any previous year (Table VI). This is directly attributed to the fact that it is our first full year with an ambulance.

The proportionate number with abscess and with peritonitis was the same, but the actual number was greater than in any previous year. As a result, we dealt with more critical cases of peritonitis during this period.

There were no deaths from the disease in any one of the three varieties, the impressive mortality rate of zero. Complications were relatively few in the total series (Table I), and there was a noticeable reduction in wound infections and secondary peritoneal abscesses, as compared to the previous years (Table II).

SUMMARY

A total of 741 patients with acute appendicitis was operated upon during the 1935 to

TABLE V.—COMPARATIVE MORTALITIES FROM OTHER HOSPITALS

	Acute Cases	Mortality %	Abscess Cases	Mortality %	Peritonitis Cases	Mortality %	Total Mortality %
Miller, et al., Cook County Hospital	629	0	23	8	281	12.8	5.4
Stafford and Sprong, Johns Hopkins	838	0	283	7.06	196	14.23	3.6
Barrow and Ochsner, Charity Hospital, New Orleans	860	0.8			179	27.3	5.3
Reid and Montanus, Cincinnati General Hospital	583	1.03	129	10.08	209	17.22	4.86
Horsley, J. S., Jr., Richmond, Va.	706	0.71			133	2.26	0.05
Davis and McLaughlin, Omaha, Nebraska	784	0.5	50	8	124	13.7	3.11
Roosevelt Hospital, New York City, 1935–40	718	0.42	80	5	147	8.8	2.1

TABLE VI.—1940

Type	Cases	Deaths	Mortality %
Acute	152	0	0
Abscess	21	0	0
Peritonitis	31	0	0
Total	204	0	0

1939 interval. The mortality rate varied from 0.53 per cent in the simple acute variety to 11.2 per cent in the perforated appendix showing peritonitis, with a total mortality of 2.7 per cent.

Sulfanilamide was applied intra-abdominally in nearly all the patients during 1940 in whom there was real or doubtful involvement of the peritoneum by infection. Complications seemed less frequent and were less severe, the drug in the dosages used had no severe toxic effects generally and failed to show any destruction of tissues locally. The only local effect noticeable was the encouraging rapidity of healing.

In conclusion we wish wholeheartedly to endorse the use of sulfanilamide intra-abdominally when indicated. We do not desire to give the impression that the mortality rate from the disease with its use will henceforth approximate zero, as we feel unusually fortunate in that there were no deaths from embolism or other conditions entirely dissociated from peritonitis. It is our firm conviction, however, that the dramatic reduction in our mortality rate during the year of 1940 was directly due to sulfanilamide.

BIBLIOGRAPHY

1. BARROW, W., and OCHSNER, A. Treatment of appendiceal peritonitis. J. Am. M. Ass., 1940, 115: 1246–1249.
2. DAVIS, H. H., and MCLAUGHLIN, C. W., JR. Results of treatment in acute appendicitis. Surg., Gynec. & Obst., 1940, 70: 713–715.
3. DRAPER, JOHN W., and KAUER, JOSEPH. By personal communication.
4. GARLOCK, J. H. Incisional hernia following operation for acute appendicitis. Surg. Clin. N. America, 1939, 19: 449–452.
5. HORSLEY, J. S., JR. Abstract of discussion. J. Am. M. Ass., 1940, 115: 1250.
6. LADD, W. E. Immediate or deferred surgery for general peritonitis associated with appendicitis in children. New England J. Med., 1938, 219: 329.
7. MILLER, FELL, BROCH, and TODD. Acute appendicitis in children. J. Am. M. Ass., 1940, 115: 1239–1242.
8. REID and MONTANUS. Appendicitis; analysis of 1153 cases at Cincinnati General Hospital. J. Am. M. Ass., 1940, 114: 307–1311.
9. STAFFORD, E. S., and SPRONG, D. H., JR. The mortality from acute appendicitis in the Johns Hopkins Hospital. J. Am. M. Ass., 1940, 115: 1242–1245.
10. WINTHROP CHEMICAL CO. By personal communication.

THE NEUROGENIC FACTOR IN INTESTINAL OBSTRUCTION

R. F. ANTONCIC, M.D., Cleveland, Ohio

HAMPDEN LAWSON, M.D., Louisville, Kentucky

THE importance of afferent nerve impulses from obstructed distended intestine is again being stressed. Braun and Borrutau were the first to postulate a neurogenic theory for death in obstruction, according to which noxious stimuli reach the brain and produce failure of vasomotor and other centers. Whipple, Stone, and Bernheim observed that the duration of life in their experimentally obstructed dogs was directly proportional to the degree of distention but considered absorption of toxins the cause of death. Dragstedt found that the toxemia was relieved and the chlorides rose in the blood when the obstructed loop was aspirated through the abdominal wall. He considered distention merely an accessory factor which damaged the intestinal mucosa permitting bacterial toxins to be absorbed. Burget et al. noted that a sick dog refusing all food would often eat eagerly 30 minutes after an obstructed loop was aspirated. He decided that death is due to loss of chlorides in the vomitus and that the vomiting is due to reflex nausea and pain from the distended loop rather than to absorption of toxins. Herrin and Meek (10) placed balloons in Thiry-Vella loops. The balloons were maintained at a constant pressure of 50 to 80 millimeters of mercury. Fourteen dogs thus treated died in 8 days. The symptoms and blood changes were those of acute intestinal obstruction. Herrin and Meek pointed out that the beneficial effect of saline injections, re-introduction of vomitus and aspiration of closed loops might all be explained by dilution, neutralization, or withdrawal of toxin. The authors thus disposed of the toxin theory since death occurred despite free drainage of Thiry-Vella loops. By administering 30 cubic centimeters of 10 per cent sodium chloride daily, these workers kept a dog alive for two 14-day periods of distention. A third period of distention without salt resulted in the death of the dog. Meek and Herrin then denervated similar draining loops. Of 8 animals thus prepared 3 endured the distention for 20, 21, and 23 days, respectively, with no symptoms and normal blood chemistry. Four others showed "undoubted protection." They concluded that distention causes reflex vomiting and inhibition of appetite and as a result death occurs from unbalanced chloride loss.

Ender and Herrin divided the jejunum 25 centimeters from the ligament of Treitz, inverted both ends, and anastomosed the distal end to the stomach or duodenum, thus producing complete simple obstruction of the jejunum. The fluid from the obstructed bowel returned to normal bowel so that there was only slight loss from vomiting. Four dogs lived 8 days (perforated), 2, 4, and 6 weeks, respectively. Of two denervated animals, one was without symptoms for 16 days and then died on the seventeenth day within a few hours of the onset of symptoms. The other dog was reported normal on the eighteenth day of obstruction. Since all dogs survived far beyond the 8 days (except the one with perforation) reported for simple jejunal obstruction, the authors concluded that the rôle of toxemia in acute obstruction seems to be of less importance than chemical or nervous factors.

Taylor, Weld, and Harrison introduced a balloon into the duodenojejunum with a bypass of heavy walled rubber tubing. In this manner the authors were able to distend the intestine with pressures of 60 to 110 millimeters of mercury without completely blocking the lumen. They showed fluoroscopically that a barium meal passed through the rigid tube beside the distended balloon. Dogs thus prepared vomited only occasionally, the blood chlorides remaining near normal; yet all died within 54 hours. However, if the segment of

From the Departments of Surgery and Physiology, University of Louisville, School of Medicine.

bowel holding the balloon was denervated, the dogs survived the distention about 72 hours, dying of peritonitis induced by balloon erosion of the gut. Taylor and his co-workers believe distention per se is the primary cause of death in intestinal obstruction, i.e., afferent nerve impulses from the distended viscus cause the vomiting, fall in pressure, and collapse of acute intestinal obstruction.

Best and Taylor stress that acute distention of even a small intestinal pocket as in Richter's hernia in which the intestinal lumen is not entirely occluded, leads to all the symptoms of intestinal obstruction. Wangensteen and Rea by excluding swallowed air (cervical esophagostomy) and preventing distention in dogs with complete occlusion of the terminal ileum spared these animals for an average of 36 days (giving 1500 cubic centimeters of 1 per cent saline daily and occasional blood transfusions). These authors concluded that the mechanical factor of distention and not a toxic factor accounts for the lethal issue in ileal obstruction.

Fine, Rosenfeld, and Gendel resected the cœliac ganglion and all the splanchnic nerves (and/or the subdiaphragmatic vagus nerves) in cats, checking the completeness of the denervation at autopsy on the death of the animals. They concluded that exclusion of the extrinsic nerve supply does not influence the survival time. However, Herrin and Meek (11) found vagotomy, splanchnicotomy, and lumbar sympathectomy permitted the distention of Thiry-Vella jejunal fistulas without any symptoms in 6 dogs. Bilateral splanchnicotomy and lumbar sympathectomy prevented vomiting and to some extent the depression, but anorexia appeared.

Our observations indicate that denervation does exert a protective effect and by using non-draining loops distended by the gas and secretion resulting from the obstruction alone, we produced the ideal medium for absorption of any specific toxin formed in intestinal obstruction.

METHODS

Obstruction of the first portion of the jejunum, 15 centimeters from the ligament of Treitz, was produced by the technique of Stone, Bernheim, and Whipple, i.e., resection of a 10 to 12 centimeter segment, inversion of the ends to form a closed loop, and then reestablishing the continuity of the gastrointestinal tract by an end-to-end anastomosis. Numerous workers have shown (6, 5, 13) that death occurs more rapidly under these conditions than if the bowel is obstructed by a single ligature at this level. Denervation of these obstructed loops was effected by dissecting out the central vessels, cutting all other structures, and painting the vessels with 20 per cent phenol in 15 dogs. Denervation was produced in 6 dogs by infiltrating the mesenteric pedicle with 95 per cent alcohol (or ether, 2 dogs).

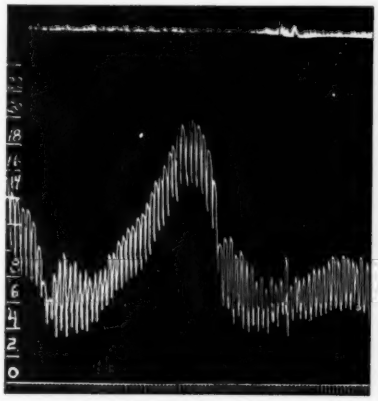


Fig. 1. Tracing of denervated non-draining jejunal loop, obstructed for 12 hours. Top tracing, respirations; timer, 4 second intervals; scale, pressure in centimeters of water.

In 6 dogs the motility of the obstructed denervated loops was studied by inserting balloons connected to water manometers and recording tracings of pressure changes on smoked paper. These observations were made on unanesthetized animals at variable intervals of obstruction.

Animals were operated upon under intraperitoneal sodium pentobarbital anesthesia. No special postoperative care was given. Water was placed in the cages next day and the stock diet the following day.

RESULTS

In the 6 dogs prepared for motility studies of denervated obstructed loops, the average of the maximum spontaneous pressures is 27

centimeters of water which is not significantly different from the average (26.8 cm.) of non-denervated obstructed loops (1). Our observations show that the motility pattern of denervated obstructed intestine is similar to non-denervated obstructed intestine. Denervation, then, does not interfere with the building of increased pressures in obstructed loops (Fig. 1).

Of 10 non-denervated control animals, all died in 36 hours to 7 days, the median being approximately 72 hours. At autopsy 7 loops were perforated and 3 were distended. Of 23 denervated dogs 11 lived and 12 died (3 to 4 days). At autopsy, in the animals which died, every loop (but one) was perforated, and death was attributed to peritonitis.

The dogs protected by denervation lived from 3 weeks to 4 months. Five dogs were killed when normal for 4 to 8 weeks. These animals did not vomit after the first day or two, ate voraciously, were active and alert. When killed, the examination revealed that 3 dogs had collapsed loops containing 10 to 20 cubic centimeters of gray mucus fluid, while two had markedly distended loops, a culture from one yielding a pure growth of streptococci (hemolytic and non-hemolytic). The contents of these loops was fecal in character, with very foul odor. Six animals died in from 3 weeks to 4 months. These were entirely normal until 1 to 2 days before death when they became listless, vomited, and refused to eat. Four dogs dead of internal herniation and volvulus apparently had acute accidents avoidable with better surgical technique. Why two animals should suddenly develop generalized gas gangrene after 3 and 4 months of normal livelihood is not apparent. It is conceivable that the anaerobic bacteria finally got a foothold and produced active infection. These dogs were tremendously distended and solid organs, like liver and spleen, were crepitant and literally bubbling with the gas.

EVALUATION

Denervation of an obstructed non-draining loop of intestine apparently will protect a dog against death for 3 or 4 months if the loop does not perforate. If perforation occurs the animal dies of peritonitis. It is not apparent why some loops perforate while others withstand marked distention for long periods. It was noted in the non-denervated controls that 3 of the dogs died with distended, non-perforated loops. It is well known that death frequently occurs from distended, discolored bowel which has not perforated. It has been shown (9) that death in closed loops, even when strangulated, can occur without bacteria in the peritoneum or the blood stream.

Herrin and Meek (10) have not disposed of the toxin theory by draining the loops to the outside since the toxin is believed by advocates of the toxin theory to be formed in the mucosa and absorbed under the influence of the distention directly into the veins and lymphatics. Our closed loops should be ideal for absorption of toxins under the pressure produced by the obstruction itself, but dogs with denervated loops lived unless the loops perforated. That denervation eliminates a neurotoxin is unlikely since animals dying of closed loop obstruction do not die of progressive paralysis; also several animals were saved with nerves spared but rendered nonconductive by ether or alcohol. That elimination of lymphatics is a protective factor is not probable since these are quickly reformed.

The data show that the protective effect of denervation is not due to altered motility.

SUMMARY

1. Dogs were prepared with closed loop obstructions, 10 serving as controls while 23 were denervated.

2. Balloon studies of intestinal motility were done in 6 unanesthetized dogs with denervated closed loop obstructions.

3. Denervation does not significantly alter the motility of obstructed loops.

4. Denervation of an obstructed non-draining jejunal loop prolongs life, dogs dying after 3 or 4 months of generalized gas gangrene. There is, therefore no evidence for the existence of a special toxin of intestinal obstruction.

REFERENCES

1. Antoncic, R. F., and Lawson, Hampden. The muscular activity of the small intestine in the dog during acute obstruction. Ann. Surg. (in press).
2. Best, C. H., and Taylor, N. B. Physiological Basis of Medical Practice. Baltimore: William Wood & Co., 1937.

3. BRAUN, W., and BORRUTAU, H. Experimental kritische untersuchungen ueber den ileustod. Deutsche Ztschr. f. Chir., 1908, 96: 544.
4. BURGET, G. Z., MARTZLOFF, K., SUCKOW, G., and THORNTON, R. C. B. Intra-loop pressure and clinical condition of animal. Arch. Surg., 1930, 21: 829.
5. COPHER, G. H., and BROOKS, B. Intestinal obstruction; an experimental study of the therapeutic value of sodium chloride. Ann. Surg., 1923, 78: 755.
6. DRAGSTEDT, L. R. Blood chemistry in intestinal obstruction. Proc. Soc. Exper. Biol. & Med., 1928, 25: 239.
7. ENDER, C. A., and HERRIN, R. C. The relative importance of toxemia in jejunal obstruction in dogs. Am. J. Physiol., 1939, 126: 485.
8. FINE, JACOB, ROSENFELD, LOUIS, and GENDEL, SAMUEL. The rôle of the nervous system in acute intestinal obstruction. Ann. Surg., 1939, 110: 111.
9. HARTWELL, J. A., HOGUET, J. P., and BEEKMAN, F. An experimental study of intestinal obstruction. Arch. Int. Med., 1914, 13: 701.
10. HERRIN, R. C., and MEEK, W. J. Distention as a factor in acute intestinal obstruction. Arch. Int. Med., 1933, 51: 152.
11. Idem. Afferent nerves excited by the distention of the jejunum in dogs. Am. J. Physiol., 1939, 126: 532.
12. STONE, H. B., BERNHEIM, B. M., and WHIPPLE, G. K. Intestinal obstruction; an investigative study of the toxic factors. Bull. Johns Hopkins Hosp., 1912, 23: 159.
13. SWEET, J. E., PEET, M. M., and HENDRIX, B. M. High intestinal stasis. Ann. Surg., 1916, 63: 720.
14. TAYLOR, N. B., WELD, C. B., and HARRISON, K. Experimental intestinal obstruction. Canad. M. A. J., 1933, 29: 227.
15. WANGENSTEEN, OWEN H., and REA, CHARLES E. The distention factor in simple intestinal obstruction. Surgery, 1939, 5: 327.
16. WHIPPLE, G. K., STONE, H. B., and BERNHEIM, B. M. Intestinal obstruction. J. Exper. Med., 1913, 17: 286.

FAT EMBOLISM

A Clinical and Experimental Study

CARLO S. SCUDERI, M.D., Ph.D., F.A.C.S., Chicago, Illinois

SINCE over 600 known references to fat embolism are found in the literature, only the high lights of the literature that pertain to the experimental and clinical work to follow will be presented. Clinically, fat embolism is very difficult to substantiate conclusively. This difficulty is really not the fault of the medical profession but is due to the nature of the disease, which makes its incontestable recognition very problematic. For this reason I have spent most of my study on the diagnostic phase of this malady. Those desiring complete reviews on the subject should refer to articles by Warthin, 1913; Scuderi (42) 1934; and Groskloss, 1936.

HISTORICAL

As early as 1669 Lower had injected milk intravenously in dogs, and this was probably the beginning of our knowledge of fat embolism.

Magendie, during the years 1821 and 1836, did some experimental work on lipemia and its effect on the circulation in animals. His description of the experimental introduction of liquid oil into the venous circulation is classic.

Zenker, 1862, observed the first fat emboli in the pulmonary capillaries of man following a severe crushing injury to a railroad worker. The pulmonary capillaries were found to contain a great many emboli of fluid fat. He thought that they occurred by aspiration through the gaping veins from the stomach of the patient.

Scriba, in 1880, reviewed all the cases up to date and then added 34 cases of his own. He also conducted animal experiments and brought forth many clinical and pathological points which had previously been obscure. Most of our modern textbooks dealing with the subject of fat embolism are based upon the statements and conclusions which he drew. However, years have shown that some of his opinions were erroneous. Of 177 cases of fat embolism which he collected, in only 14 instances could fat embolism be regarded as the cause of death, and some of these he regarded as doubtful.

Lehman and Moore (1927) by *in vitro* experiments showed that histamine, extracted from necrotic muscles, produced a very rapid disintegration of the fat emulsion of normal blood serum. They concluded that fat embolism might be readily produced in the bone marrow on a non-traumatic basis purely by the absorption of histamine, from injured body tissue, into the blood stream. They also found that intravenous ether produces fat embolism of the lung by dissolving the normal emulsified fat of the lungs, and, when the ether vapor tension is lowered by evaporation into the alveoli, the free fat becomes visible microscopically in the blood.

ETIOLOGY

The experimental work done on the etiology of fat embolism has been considerable and, in many instances, has led to much contradiction and confusion.

Males are many more times affected than females, the proportion being about 8 to 1. The youngest case on record, a newborn, was reported by Nicod. The greatest incidence is during the fourth decade of life. Rarely does fat embolism occur in children because the fat in the bone marrow is insufficient up to the fourteenth year (Speed). Landois, in an excellent article on the subject, states that he found mostly palmitin and stearin in children and infants, with a smaller proportion of the more fluid olein. At body temperature oleic acid is quite fluid and is more easily absorbed than the more viscous palmitic and stearic acids. For this reason fat embolism is not so common in children.

From the University of Illinois, College of Medicine.

It appears as though alcoholics are more predisposed than nonalcoholics. Perhaps this is due to the instability of the fat emulsion in the serum produced by the frequent dilution with the fatty solvent after a "debauche" (Cubbins).

Lehman and Moore calculated the amount of fat in the bone marrow of a femur and found it to be approximately 65 cubic centimeters. By experimental study with cottonseed oil they found that, should man be able to tolerate as much oil in the blood stream as a dog, 120 cubic centimeters would be required for a lethal outcome. This is based on two assumptions: first, that cottonseed oil does not materially differ from bone marrow fat; and, second, that man, as well as dogs, can tolerate free fat in the blood. If this be true, all the fat in the bone marrow of a femur could be well tolerated. After a great deal of controversy as to whether the fat is carried by the blood or lymph vessels, the present opinion seems to be that most of it is carried by the veins while a smaller part may be carried by the lymphatics.

It is interesting to note that experimental animals can be made to build up a resistance to experimental fat embolism by repeated small injections of fat. This work was done primarily by Paul and Windholz, and later by Domanig. They found that such animals could withstand many times the lethal dose. No fat droplets could be found free in the blood serum of these animals. Evidently they are rapidly destroyed by a newly formed, unknown substance.

PATHOGENESIS AND PATHOLOGY

After the injury to the bone marrow fat or adipose tissue, there is a disintegration of the supporting fibrous tissue with liberation of the fat. Naturally there are ruptured blood vessels in the vicinity of the injury. The arteries squirt more blood into the area, thereby increasing the pressure, while the veins remain open and absorb the fatty mixture by venous suction (Miloslavich), particularly if their consistency is more or less fluid.

Gauss (20) brings out the point that fat embolism is more common in fractures than in any other condition because the veins are encased in a bony wall and hence cannot collapse as elsewhere in the body; thus they remain wide open for the admittance of the fatty mixture. This process may take place immediately or proceed for some time until coagulation occurs. The pathology of this condition involves all the organs and is too well known by all to be discussed in this very brief résumé.

Lehman and McNattin found at postmortem examination that fat embolism is present in the lungs of about 50 per cent of unselected cases. These men have conclusively shown that anatomically the diagnosis of fat embolism as the cause of death cannot be safely made.

Wright found at postmortem examination fat embolism present in 52 of 100 consecutive cases, in the majority of which patients did not suffer from fractures or contusions from falls or accidents. This author also helps to substantiate the contention that postmortem findings of fat embolism are not pathognomonic evidence of violence.

Carrara found fat embolism present in 22 per cent of cardiovascular renal diseases and 44 per cent of burns. Catsaras reported fat embolism in the lungs of 18 of 67 cases of post-influenzal pneumonia. To add to the already great confusion on the subject, acidosis, phlegmonous gastritis, acute pancreatitis, chronic tuberculosis, menstrual suppression, hepatitis, splenitis, and tuberculous pneumonia have been mentioned. In fact, almost all diseases, poisonings, and injections to which the body has been subjected have been reported in the literature as having caused fat embolism at one time or another.

Vance, in 1931, wrote a very comprehensive paper on fat embolism from a pathological viewpoint, which is a classic on the present literature on the subject.

SYMPTOMS

There is no clinical correspondence between the apparent injury and the degree of resulting lipemia. Injuries which are apparently identical may in one individual be followed by a fatal lipemia, while in another individual the same injuries may cause but a slight disturbance.

The onset may be sudden, within a few hours of the injury, but usually does not become manifest until the third or fourth day. Once the symptoms set in, they may vary from a slight irritability and excitability of the patient to maniacal periods associated with high grade delirium and death. The symptoms, if watched carefully, have a tendency to be cyclic, corresponding to the emboli passing from the pulmonic circulation to the systemic, and gradually returning. Many of these cases appear to be doing nicely when gradually they begin to show some signs of nervousness and excitability. At this time the pulse and temperature begin to show a slight rise. The respirations show a more rapid rise than the pulse, and even early in the symptomatology may be dyspneic. As more capillaries are obstructed in the lungs, the dyspnea increases correspondingly. Cyanosis may or may not appear, depending on the extent of pulmonary impairment. Gradually a passive congestion occurs in the lungs and moist râles are audible over the bases. A cough begins to appear and is of a productive nature, rarely blood-stained, however. For this reason, many such cases are diagnosed as bronchopneumonia.

As the pulmonary arterial pressure increases, the heart must beat faster in order to overcome the circulatory resistance. The pulse becomes faster and stronger, and the blood pressure begins to rise. Should the resistance in the pulmonic circulation increase or remain great, the heart before long begins to weaken. Its rate increases while its force decreases. The blood pressure correspondingly begins to fall. Should some of the emboli lodge in the coronary vessels, then the cardiac failure comes on much more quickly. Before long, the pulse becomes imperceptible, the arterial pressure falls, the venous pressure rises and the picture of deep shock and cardiac failure appears.

The temperature varies from subnormal to 106 to 107 degrees F., depending on whether or not the heat-regulating center is disturbed by the emboli. The usual temperature, during the height of the disease, is about 103 degrees. In terminal cases the temperature often rises much higher.

Petechial hemorrhages (Ryerson in 1916) may appear in the skin, as in any other disease in which the embolic phenomena predominate. However, due to the fact that the capillaries are not actually occluded, as in bacterial endocarditis, but the circulation is greatly slowed down because of the increased viscosity of the blood (Gauss, 19), they are rare. LeCount and Gauss published the results in 14 cases of death following fat embolism, upon which postmortem examinations had been done. A study of the clinical symptoms of these cases is very instructive, as it gives us some idea of what occurs in milder cases which do not have an *exitus lethalis*.

All of these patients passed from consciousness to a restless stage. In 12, this took the form of delirium, 11 becoming so violent as to require restraint. Eleven passed from delirium to the comatose state. In all 14 cases dyspnea was present, and also an associated increase in respiratory rate, the average being 53 respirations per minute. Two cases developed Cheyne-Stokes respiration; 4 suffered from air hunger; 2 developed a marked cough. The pulse became weak and shallow and averaged 153 per minute. Involuntary passage of urine and feces occurred in 12, and in the 2 others the records were incomplete. At the time of admission the temperature was either normal or subnormal, and then rose to an average of 105.2 degrees F. for the 14 cases. The time that they lived varied from 2 to 17 days, with an average of 6 days.

DIAGNOSIS

The majority of cases of fat embolism are so mild that they do not cause symptoms, or so severe that death results in a few days from involvement of the lungs or the brain. During life the diagnosis of fat embolism is justified only if there is a history of an injury, with the typical clinical manifestations.

The incubation period varies from a few hours from the time of accident to 3 or 4 days. It is a good point to remember Dennis' rule in this respect, regardless of the exceptions: shock, 3 hours; fat embolism, 3 days; pulmonary embolism, 3 weeks (Speed).

Additional confirmatory signs are the presence of fat in the urine, the demonstration of

fat emboli in the retinal vessels by the ophthalmoscope, and the appearance of petechial hemorrhages in the chest, shoulders, and neck. The presence of the large circular cells of Elting and Martin or the fat globules of Warthin in the sputum are not pathognomonic signs, as they are found in conditions other than fat embolism. As a rule, fat embolism is rarely diagnosed from clinical signs and symptoms; it is most often discovered accidentally at necropsy.

In the differential diagnosis delirium tremens, skull fractures, bronchopneumonia, and shock must be most seriously considered.

PROGNOSIS

The prognosis in fat embolism should always be reserved because some of the patients who appear to be coming along well suddenly grow worse and die. As to life, most of the patients recover, but due to the fact that only the fatal or very sick cases are diagnosed and the mild cases overlooked, most people have the reverse idea.

TREATMENT

As fat embolism in fractures is not of common occurrence, and when it does occur is rarely diagnosed, one can understand why reports regarding the treatment of this complication are not very illuminating. Grondahl states that a terminal result occurs in but 1 of every 3,000 cases of fracture, and that death attributed to fat embolism in fracture cases occurs in only 1 per cent of the cases.

Much experimental work has been done on the prophylaxis, with much forethought and logical thinking. Wells, Ryerson, and Caldwell and Huber have shown that a tourniquet, if used during the operation or manipulation, reduces the possibility to a minimum, especially if it is allowed to remain in place for an hour after the operation. Simonds found that etherized dogs were more susceptible to fat embolism than were those anesthetized by non-fat solvents. This is a point of some importance and if another anesthetic, which is not a fat solvent, can be used as efficiently and safely, it should be given preference.

Warthin advises the following prophylactic management: 1. Avoidance of unnecessary or rough handling of patients. 2. Immediate splinting and early reduction of all fractures (Tanton). 3. In orthopedic operations use of a saw in preference to the chisel, if possible (Lexer). 4. Slow removal of Esmarch's bandage (Buerger, Aberle).

Reiner advises canaliculizing the vein, allowing the first blood after removal of the constrictor to flow out. Czerny, and 50 years later Wegelin, also advocated the injection of sodium carbonate, probably with the idea of forming a soluble soap. This method has fortunately received but little support. All experimental animals died under this regimen.

The active treatment of this condition is very poor, and many of the suggested methods are not only theoretically, but also practically, in error.

Czerny advises venesection to lessen the venous congestion. Schanz believes physiological salt solution both intravenously and by hypodermoclysis to be of benefit, while Bissell believes that such a procedure is contra-indicated because of increased pressure to the right heart.

Wilms suggested drainage of the thoracic duct. Fritsche found experimentally that if this was done at the first appearance of the symptoms it helped. Grondahl found that even ligation of the femoral vein and removal of the inguinal glands did not prevent fat embolism.

Wilms also advised incising the area of fracture and combating its origin by evacuating the blood and fat.

Pituitrin, pituglandol, caffeine, coramin, morphine, and sympatol have been suggested in the active treatment, as they have been found both experimentally and clinically to produce a steady fall of blood fat.

VALUE OF BLOOD CHEMISTRY AND PHYSICAL MEANS OF QUANTITATIVE BLOOD FAT DETERMINATION

Since the problem of fat embolism has to do with the presence of fat droplets in the blood stream, it was thought that quantitative blood fat determinations would be of material aid in its diagnosis. For this reason the known methods were looked up and studied in great detail.

Kumagawa and Suto described a saponification method in 1908. Bang, in 1918, described an extraction method, which, however, is not accurate enough for a truly scientific method. Bloor, Pelkan and Allen (6) first brought the nephelometric method to the foreground in 1922. Later in 1928 Bloor (5) published an improved method. Stoddard and Drury described a titration method in 1929.

After a careful study, counsel was sought from several very well known physiological chemists, and all agreed that the methods were beyond the capacity (or ability) of the average part-time chemist, and even when the determinations were done in well equipped laboratories by properly trained men, the variations were too great to be of real diagnostic value. For the present at least, the outlook along these lines is unfavorable.

Clinical investigation in the serological department of the Cook County Hospital has revealed many blood serums of almost cream-like appearance. These were found in diabetic comas, lipoid nephrosis, and lactating postpartum women. In spite of the fat content of the blood having reached this startling height, these cases revealed no manifestations of fat embolism. Some investigators have found diabetic coma cases to have reached a concentration of total lipoids in the blood of 26 per cent (Bantin), compared with the normal of 0.4 per cent. These observations, therefore, have conclusively proved to the author that it is not the total fat content of the blood which we should be interested in, but the state in which this fat is found. Should it be in the form of a stable emulsion, no fat droplets are present in the blood, hence no embolism can occur. On the other hand, the corpuscular fat content is of all importance as it causes the occlusion of the vessels giving the embolic phenomena. Unfortunately, only 5 per cent of the total fat content of the blood is found in this form. If one considers that the total fat content, as has been stated before, is only 0.4 per cent, the figure of the corpuscular percentage almost approximates zero. Therefore, it stands to reason that any total chemical method for determining increases or decreases of this element would be far beyond the scope of quantitative chemical determinations as the percentage of error by our best present day methods would be too great.

Other fields of experimental work were searched for possible aid in these determinations. The use of the spectroscope was suggested. However, it has been stated that the fat concentration was too small to produce any appreciable variations.

At a later date the possibility of the use of electroconductivity to determine fat content changes in blood serum was considered, but this method and also the use of the polariscope has been found to be of negative value, and henceforth dropped.

RESULTS OF DARK FIELD EXAMINATIONS OF THE BLOOD AND FRESH SMEARS OF RECENT FRACTURES AND CONTROL CASES

Edmunds first described the dark field examination of the blood for fat particles in 1877. Further work along these lines was carried on by Neumann in 1907. Gage and Fish (18) in 1924 published a most excellent article upon this subject, on investigative work on fat absorption and metabolism in the lower animals. Gage (17) was the first to give these microscopic particles the name of chylomicrons, 1920, meaning that they are one micron in diameter and are composed of chyle.

The study of 25 miscellaneous blood serums from the medical wards of the Cook County Hospital, was undertaken as a control study. No variations from the normal were found. Several cream-like blood specimens from a lactating postpartum woman revealed a few interesting observations. In spite of a cholesterol of 335 milligrams, and a milky appearing serum, no actual fat droplets could be found, a fact showing the marvelous stability of a serum fat emulsion.

As the average blood cell is 10 microns in diameter, it has been estimated that in order to occlude the finer capillaries of the lung the fat droplet must be at least 12 to 15 microns in diameter. In none of the control cases was this found.

In order to show the feasibility of this diagnostic method in embolic cases, olive oil was injected intravenously in a dog. Five cubic centimeters were used, and it was injected slowly. Two minutes later, with a clean

syringe and needle, 1 cubic centimeter of blood was removed from the opposite leg, and a drop was examined under the dark field. Large ameba-shaped droplets of olive oil could be easily demonstrated, at least twice the diameter of an erythrocyte.

Twenty-five fresh fracture cases from the service of Dr. William R. Cubbins were now selected. All were suffering from major fractures from 3 to 144 hours from the time of accident. One whole blood and one centrifuged serum specimen of each patient was examined. No difference was found between the specimens except that the centrifuged serum was easier to examine due to the lack of interference of a large number of blood cells.

No actual fat droplets were found. I am of the opinion that patients suffering from true fat embolism will show droplets in great number, and that this method will be of a real diagnostic aid.

TECHNIQUE OF URINE ANALYSIS IN FAT EMBOLISM

In the study of this problem, several hundred urine specimens have been examined for the presence of fat in the urine of suspected cases. After a period of time, it was found that this apparently simple investigative phase of the problem offered an interesting physical phenomenon which heretofore has evidently not been emphasized, and for this reason I undertook its investigation.

That fat is excreted by the kidneys into the urine in cases suffering from fat embolism is well known and often spoken of in the literature. Unfortunately, however, its detection is difficult because of one very elementary physical phenomenon, and that is that the fat droplets float on the surface of the urine, and therefore are not excreted from the bladder unless the last few cubic centimeters of urine are expressed. For this reason many urines examined which contain fat are negative because of this simple oversight.

To prove conclusively this contention, two flasks were used to carry out this experiment *in vitro*. The setup used is illustrated in Figure 1. The flask above represents the kidney, while the one below, the bladder. These are

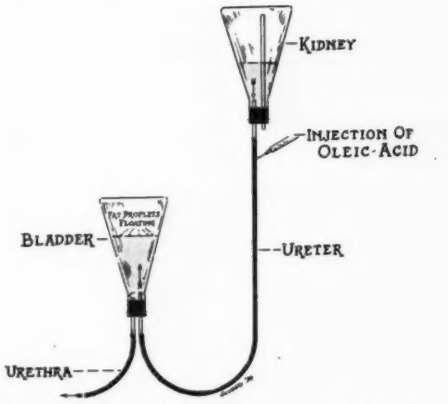


Fig. 1. Set-up used in experiments. Genito-urinary system *in vitro*.

connected by a rubber tube representing the ureter. A second tube from the lower flask represents the urethra. The fluid was permitted to run very slowly from the top flask to the lower, and fine droplets of oleic acid and also olive oil were injected into the tube close to the top flask with a hypodermic syringe. In this manner there existed a visual genito-urinary system. It was noticed that as the fluid accumulated in the lower flask, the fat droplets rose to the top. (In both the *in vitro* and clinical experiments 2 cubic centimeters of oleic acid were used, divided into small droplets by simple shaking with water.)

After the lower flask was filled, the pinch clamp on the rubber tube representing the urethra was removed, and the fluid permitted to flow out. The entire contents of the flask, with the exception of the last few cubic centimeters of fluid, were absolutely fat free. Both urine and plain tap water were used as the fluid in the *in vitro* experiment, and the physical phenomenon was found to be the same.

In order to prove conclusively what was so well demonstrated *in vitro*, the experiment was carried out in the human. With the co-operation of Dr. P. Nelson of the urology department, the pelvis of the kidney was injected with 2 cubic centimeters of sterile oleic acid in cases following retrograde pyelography. Four cases were used, 2 males and 2 females.

Two to 3 hours after the fat injection into the pelvis of the kidney, the males were in-

TABLE I.

Type of fracture		Number of hours since accident	
Tibia	20	1– 24	11
Femur	14	24– 48	8
Humerus	7	48– 72	6
Fibula	5	72– 96	9
Patella	1	96–120	6
Forearm both bones	1	120–144	3
Pelvis	1	144–168	7
Ribs	1	Total cases	50
Total cases	50		

Number of cases showing fat		Number of cases showing urine casts
Urine	0	9 cases from 1–2 to 1–12 L.P.F. in centrifuged specimens.
Blood serum	0	

structed to pass the urine into 5 to 7 flasks, urinating not more than two fingers' depth in each. In both cases, the last flask contained all of the oleic acid, while the others were absolutely fat free. Due to the difficulty of collecting the divided urine specimens in the female, they were catheterized with glass catheters. In both cases the urine flow ceased without evidence of any fat floating in the flasks, but when the patient was compelled to sit up, then the oleic acid filled the glass catheter and not another drop of urine was expressible.

A CONTROL STUDY OF THE URINE AND BLOOD EXAMINATION IN NON-EMBOLIC CASES

As far as one is able to determine from the literature, the study of the urine and blood serum in normal cases and fresh fractures has never been done. For this reason the following work has been carried on to see whether or not free fat is found in normal control cases.

Two hundred miscellaneous hospital cases were used for the urine examination. In this series only ambulatory male patients were used because of the greater ease in collecting the urine specimen. Great care was exercised in this work to have the patient empty his bladder completely. Unless all of the urine of the bladder is collected, the floating fat droplets will not be expelled, and hence the urine examination would convey the wrong conclusion.

The urine specimens were collected and placed in a cold place overnight. The next morning the surface of the urine would be carefully examined for floating fat droplets. Any questionable droplets were removed, stained with Sudan III, and examined microscopically. In this entire series not one case showed any free fat.

The serology department of the Cook County Hospital was kind enough to permit the unlimited use of the blood serums sent to them for Wassermann tests. Each specimen was labeled, centrifuged, and then placed in the refrigerator overnight. The following morning each tube was carefully examined. All questionable droplets or débris were stained and examined microscopically. On 5 occasions definite fat droplets were found floating on the surface. However, the findings proved only that the needles had been kept in liquid petrolatum in each case, and evidently the boiling did not dislodge the oil from the inside of the needle, but when the blood was drawn for examination the oil found its way into the specimen.

Eleven of these cases showed a chylous emulsion which rapidly found its way to the surface. This is physiological, as any blood serum drawn within an hour or two after the ingestion of any fatty material presents this phenomenon. In each of the cases cited herein, the contention mentioned was found to be correct.

Fifty fresh fracture cases were next studied. Only male patients suffering from major fractures were examined. The duration of the fractures was from 1 to 7 days. The urine was collected by having the patient in either the sitting or standing position, and then having him completely evacuate the bladder. Ten cubic centimeters of blood were then drawn from the arm and both specimens were centrifuged and examined. The urine residue was stained with Sudan III and examined microscopically. Occasionally casts were found, but in not one instance could fatty casts be found as Riedel described as being present in the urine of 42 per cent of cases with fresh fractures.

The casts were no more numerous nor in any way different from the casts found in any group of urine specimens. Not one specimen of blood serum or urine showed any evidence of free fat droplets. A résumé of these cases is given in Table I.

FAT EMBOLISM
THE VALUE OF CHEST PLATES IN ITS DIAGNOSIS
AN EXPERIMENTAL STUDY

Jirka and Scuderi in 1936 showed for the first time the value of chest plates in the diagnosis of fat embolism.

Eleven dogs were used in the experiments, selecting whenever possible an animal weighing close to 12.5 kilograms. Sterile oleic acid was given intravenously to 6, and sterile olive oil to 5 of the animals. Varying doses were used in each experiment.

Due to the research of Landois, who found that olein was the largest component of bone marrow fat, it was decided to try both oleic acid and olive oil in our experiments. The former, being the acid of the trioleate and easily obtainable, was first used. However, as it is toxic and probably unites with the alkaline radicals in the blood stream to form a soap in the chemical sense of the term, olive oil, which is a neutral oil and non-toxic in smaller quantities, was used as a control. It was found that 0.33 cubic centimeter of oleic acid per kilogram of body weight was sufficient to produce death, while 2.2 cubic centimeters of olive oil per kilogram of body weight were required to produce death in dogs. The physical properties of both were similar in that their viscosities were nearly equal and both produced like droplets when emulsified. First the technique for x-ray films of the chest of a dog had to be worked out. Once the plates began to be uniformly good, the oily substances were injected. By taking films before and after the injections, we were able to compare the lung fields, taken in each instance with the same technique.

Figure 2a shows the normal lung field of one of the animals. The lungs are relatively clear, except for the usual hilus clouding. Figure 2b was taken twenty minutes after the injection of 6 cubic centimeters of sterile oleic acid. The lungs fields now appear more or less cloudy, of a diffuse, even nature. No patches or increased opacities are noted. The heart shows no enlargement when measured by the superimposition of the films. The following morning the dog was found dead, *rigor mortis* being present. The thoracic organs were removed and roentgenographed *in toto*. The lungs showed the lack of air. Gross appearance and cut section simulated liver, or the hepatization found in cases of bilateral pneumonia. Palpation revealed no crepitant areas.

Microscopic sections were made and were examined by Dr. Benjamin Nieman of the pathology department of the Cook County Hospital. He described the lungs as being typical of a drowned animal, due to the marked edema of the epithelial cells lining the alveoli, and the clear serous filled alveoli. With Sudan III stain the fat filled capillaries were readily demonstrated.

Figure 3a is of another animal prior to any experimentation. Twenty-five hours after the injection of 2 cubic centimeters of sterile oleic acid, the second film was exposed, Figure 3b. The animal at that time appeared perfectly well and quite normal in every respect. The identical technique was used in both films. Close examination reveals the same diffuse haziness of both lung fields, as seen in the other set of pictures.

Figure 4a shows the normal lung field of another experimental animal. Ten cubic centimeters of sterile olive oil were injected intravenously and 48 hours later another checkup plate was taken, Figure 4b. The same diffuse cloudiness of both lung fields, so characteristically found in all the experiments, was likewise present. The upper lobes show the pathological condition clearly.

From 2 to 12 cubic centimeters of oleic acid were used in the first 6 animals, while from 2 to 20 cubic centimeters of olive oil were used in the last 5.

The animals receiving less than the lethal doses of oleic acid, 4 cubic centimeters, showed evidence of pulmonary irritation for several days. All of these animals had apparent colds, sniffling and coughing periodically; otherwise they appeared normal.

The animals receiving up to 20 cubic centimeters of sterile olive oil showed no evidence whatsoever of any pulmonary irritation or malaise and had no apparent ill effects from the experiments. One of the animals, after having received 20 cubic centimeters of olive oil, became ataxic and had great difficulty in controlling the extremities, although otherwise it appeared normal. The inebriation

stage lasted about 10 minutes, then he ran around and was normal. This period probably existed while the fat droplets were interfering with the cranial circulation.

One must not lose sight of the fact that fat embolism is not a true embolism in the sense of a permanent occlusion of a vessel, but simply a retardation of the blood flow through a capillary while the oil droplets become elongated and are slowly forced from the arterial to the venous side of the circulation.

THE SIZZLE TEST FOR FAT IN THE URINE

Accidentally, in using the platinum loop for the taking of microscopic specimens, the author noted that whenever fat droplets were present, a sizzling and popping occurred when the loop was heated over an open flame. When no sizzling and popping occurred, only rarely were fat droplets ever found in the microscopic examinations.

This observation was investigated further in order to determine the accuracy of this method for fat determinations.

One drop of olive oil was thoroughly emulsified into increasing dilutions of water, and the sizzle test tried. The test was very definite until the dilution reached 1 drop to 80 cubic centimeters of water, after which the sizzling and popping was not constant. This represented a dilution of 1:1400 to 1:1600.

Dilutions of 1 drop in 80 to 120 cubic centimeters gave an occasional pop with a discoloration of the flame. One drop in 130 to 150 cubic centimeters just gave a discoloration of the flame; this, of course, was of no value.

A bacteriologist has since informed me that she uses this method for hurriedly finding out whether or not any diphtheria organisms are present in a smear, because if they are, the heating ignites the fatty capsule producing a characteristic popping. Of course, she always checked this observation with a culture.

Normal human and dog urines were tested and found to be approximately the same as the tests run with plain water. When no fat was added, only a yellowish blue discoloration of the flame took place.

This simple test requires no special training, nor equipment, and its efficiency makes it almost as accurate as a microscopic examination.

THE TECHNIQUE OF SUDAN III STAINING OF URINE AND BLOOD SPECIMENS

The staining of urine and blood specimens with Sudan III for examination turned out to be a stumbling block in many of the observations because a number of the details which were important were not appreciated. Until many control studies were undertaken to determine the exact technique, many experiments had to be repeated. The conclusions were as follows: (1) The stain must be fresh; (2) a high concentration of the dye is necessary to stain the fat droplets; (3) the stain must be permitted to act on the fat for at least 5 minutes in order to stain it well; (4) orange droplets less than 3 to 4 microns in diameter are either contamination or undissolved stain; (5) a drop of stain must be added directly to the slide and not to a test tube specimen.

GARDINOL AND DECHOLIN SODIUM AS THERAPEUTIC AGENTS

Gardinol (sodium lauryl alcohol sulphonate), made by DuPont, is probably one of the most efficient emulsifiers known. A few drops added to an oily mixture produces a very fine and relatively stable emulsion with but little agitation. A study of its value in diagnosis has been described elsewhere.

From previous experiments it was found that 2.2 cubic centimeters of olive oil per kilogram body weight was the minimal lethal dose in dogs. Two animals of about the same size were chosen, weighing 10.1 kilograms and 8.2 kilograms. Both received a lethal dose of intravenous olive oil, 2.2 cubic centimeters per kilogram body weight. Five minutes later when the dogs were very dyspneic, one received 20 cubic centimeters of 2 per cent gardinol and almost immediately the dyspnea subsided but within 10 minutes it had returned to almost the same degree. Twenty cubic centimeters more of 2 per cent gardinol was given, but the animal was still very ill. The second animal which had received only the olive oil was *in extremis*. Both were observed for 1 hour, the gardinol treated animal being in much better physical condition; however, it was still very ill. The next morning both were found dead. The un-

treated dog was in *rigor mortis* while the gardinol treated animal was still limp.

Postmortem examination of both animals revealed a bloody, frothy exudate in both lungs with patches of massive consolidation, more so in the untreated animal. The kidneys, liver, spleen, and intestine showed diffuse areas of hemorrhagic mottling throughout the organs. Specimens were taken and studied microscopically. Massive occlusion of the vessels with droplets of fat was visible in all the sections.

Six more dogs were injected with 2.2 cubic centimeters of olive oil per kilogram and each received 20 cubic centimeters of 2 per cent gardinol immediately after the olive oil was given, and 10 minutes later. All animals died within 12 hours.

In vitro, this quantity of gardinol, if properly mixed with 20 to 30 cubic centimeters of olive oil, would produce a very fine and durable emulsion. There is no doubt in the mind of the author that some reaction occurs in the body to prevent the same mechanism *in vivo*.

Since bile salts are emulsifiers and saponifiers of fat, many experimenters have entertained the idea that the injection of a bile salt, provided that it was not very toxic, should help to break up the occluding fat, thereby clearing the obstructed vessels of the interfering fat droplets. Until the commercial preparation of decholin sodium was offered, the bile salts were too toxic to be of any real value. Decholin sodium (sodium dehydrocholate) has been recommended by Paul deHaen Chemical Company as a therapeutic agent in the treatment of fat embolism. It is made by the addition of sodium hydroxide to dehydrocholic acid. This was first synthesized by Hammerstein in 1881. This preparation is the least toxic of the bile salts. Rappert did some experimental work with it and recommended it most highly both as a therapeutic and diagnostic agent. In repeating his work I have unfortunately been unable to corroborate his findings.

As has been stated elsewhere 2.2 cubic centimeters of olive oil per kilogram body weight is the minimal lethal dose in dogs if given intravenously. Varying doses of decholin sodium were employed before, during, and after the lethal quantity of olive oil. In no instance were any of the animals saved. As far as the author is concerned, decholin sodium is of no value in the therapy of fat embolism.

THE MECHANISM OF FAT EXCRETION THROUGH THE KIDNEYS

The author has been unable to find any reference to previous work done on the mechanism of fat excretion through the kidneys. Numerous cases of chylemia have been reported, but all have been purely clinical in their presentation.

This problem was undertaken because of its relationship to the diagnosis of fat embolism in traumatic cases. Before approaching the problem it was necessary to determine whether or not normal dogs under varied physiological conditions ever excreted fat in the urine.

The urine of two normal dogs was examined and found to be negative for fat by microscopic tests described later. Two dogs which had been given one pint of cream, one 3 and the other 6 hours previous to the urine examination, had no fat in the urine. Two other dogs which were being starved in other experiments also showed negative results. The kidneys of these 6 animals were sectioned and stained with Sudan III. In none was there any evidence of fat droplets in either the glomeruli or tubules.

Knowing that dogs under varied physiological conditions did not excrete fat in the urine, its presence should be considered abnormal.

All the animals in the following experiments were operated upon under nembutal anesthesia.

The pedicle of one kidney was isolated through a loin incision and the renal artery carefully dissected from the surrounding tissues. The ureter was then traced to the bladder and cut free, the end being cannulized with a glass cannula. The cannula was then brought out through the anterior abdominal wall through a stab wound and fixed in place. With a very fine needle the fat was injected into the renal artery. When the injection was completed, the renal artery had to be carefully clamped in the longitudinal axis to pre-

vent loss of blood through the needle hole and still not completely occlude the renal artery. Occlusion of the artery would obviously result in cessation of the urinary flow from the isolated kidney. A miniature paper clip was used for this purpose, having a small spring in it. After the fat had been injected, the kidney was placed back in the loin and the wound sutured.

Both dog bone marrow fat and olive oil were used in various physical forms. Olive oil or bone marrow fat was used in some, emulsified fat in others. As emulsifiers, plain water with a little soap, and also solutions of gardinol were tried. The results were uniformly the same. In order to increase the urinary output, intravenous Ringer's solution from 200 to 300 cubic centimeters with 1 gram of caffeine, or 200 to 250 cubic centimeters of 2 per cent urea in physiological salt solution were given intravenously. The urine was collected from the cannula in the anterior abdominal wall and examined by centrifuging it for 15 minutes at high speed, then staining the supernatant liquid with Sudan III. A film from the surface of the urine was examined under the microscope for the orange colored spherical droplets of fat. When present these varied in size from 3 to 8 microns in diameter.

Results of experiments on a series of dogs and Louisiana bull frogs showed that the intravascular fat is excreted through the kidneys providing that 0.75 cubic centimeters or more fat per kilogram body weight is injected. The fat is excreted not through the glomeruli but only through the tubules. These experiments have been described by the author in detail in a recent article (43).

STUDIES ON THE SURFACE TENSION OF BLOOD SERUM

In the search for methods of accurately diagnosing fat embolism the effect of the fat droplets on the blood serum was studied. It is a well known fact that the mixture of liquids of different specific gravity, or the addition of inert particles to a liquid, produces definite changes in the surface tension. With this thought in mind, experiments both *in vitro* and *in vivo* were conducted.

In order to eliminate the most common factors that produce errors, the eye glass and the platinum loop of the DuNouy tensiometer were washed first with soap and water followed by ether. They were never used until thoroughly dried.

The average of ten determinations was computed and found to be as follows: Control studies at room temperature—water, 85.8 dynes; human serum, 90.5 dynes; dog serum, 90.4 dynes.

Dogs were subjected to increasing doses of olive oil given intravenously. After a few minutes, venous blood was withdrawn from the opposite leg and the blood serum collected by centrifuging the specimen.

Two of the experiments were as follows:

Experiment 6. Normal blood serum reading of this dog was 90.4 dynes. One cubic centimeter of olive oil per kilogram body weight was injected, a total of 6.6 cubic centimeters being used. Reading after olive oil was 90.7 dynes.

Experiment 7. Normal blood serum reading of this dog was 88.5 dynes. One cubic centimeter of olive oil per kilogram body weight was injected, a total of 8.63 cubic centimeters being given. Reading after olive oil was 86.6 dynes.

One cubic centimeter of olive oil per kilogram body weight is about one-half the lethal dosage; in man a comparable amount would be 70 to 75 cubic centimeters. These two determinations showed but little difference in the readings. Other experiments running up to a lethal dosage (2.2 cubic centimeters of olive oil per kilogram body weight) showed very little change in the surface tension determinations. Probably many of the olive oil droplets were being held back by the small capillaries of the body and for that reason many of the droplets were not to be found in the general blood stream as we had anticipated.

Further studies were made on the variables produced by olive oil in blood serums *in vitro*. The results were as follows: ratio 151 cubic centimeters per 5000 cubic centimeters of blood—(lethal dose in man), 82.75 dynes; ratio 224 cubic centimeters per 5000 cubic centimeters of blood—77.75 dynes.

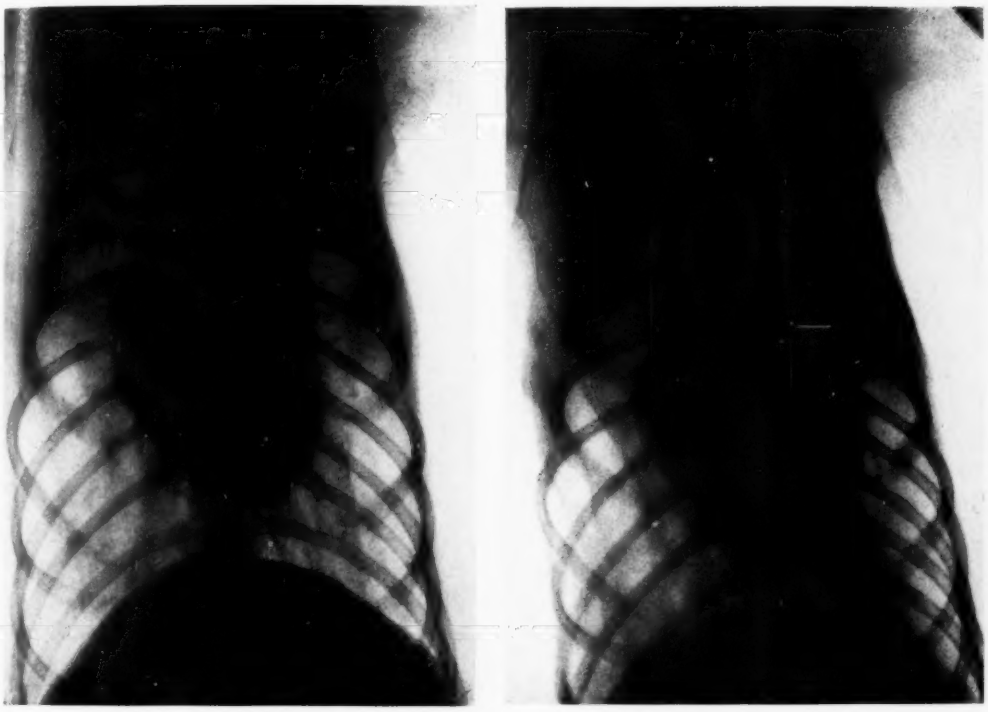


Fig. 2. a, left, Normal lung field; b, 20 minutes after injection of 6 cubic centimeters of oleic acid.

Provided that the temperature remained constant and that the specimen did not stand too long, the difference *in vitro* did show an appreciable change provided that larger quantities of olive oil were used.

The fact that the surface tension determinations varied with variations of temperature and standing of the specimen only occurred to the author after a number of confusing determinations on the same specimen during the same day. This aspect of the problem was easily gone into and was readily solved. The findings were as follows:

VARIABLES PRODUCED BY STANDING

pecimen	Surface tension	After 20 minutes' standing
No. 10	78.25 dynes	80.5 dynes
No. 11	78.35 dynes	81.5 dynes

The variation produced by standing alone would be enough to counteract any possible accuracy of the method. A far more interesting variation was observed with temperature changes. Variations of about 35 degrees of temperature produced around 8 dynes variation in the surface tension. The results were as follows:

TEMPERATURE CHANGES USING SAME SERUM

	Degrees C.	Dynes
Serum No. 3 (without oil)	21.8	88.75
	38.0	86.0
	49.0	83.5
	55.0	81
Serum No. 4	21.8	88
	36.5	84
	46.0	83
	57.0	80

These short experiments showed that the numerous variables are too great to be of any real diagnostic value even if the *in vivo* experiments were as promising as the *in vitro* ones.

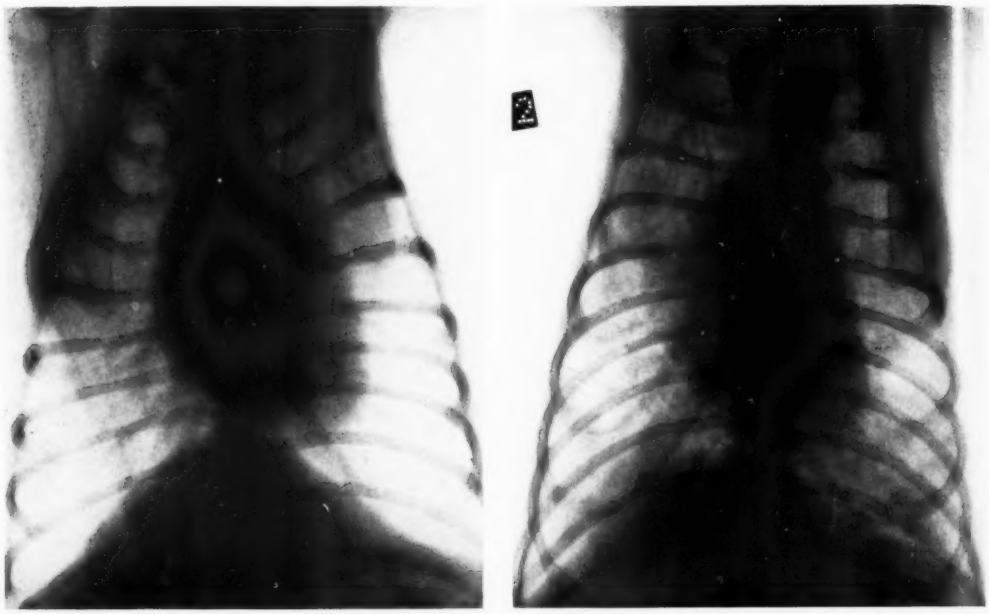


Fig. 3. a, left, Prior to experimentation; b, 25 hours after injection of 2 cubic centimeters of sterile oleic acid.

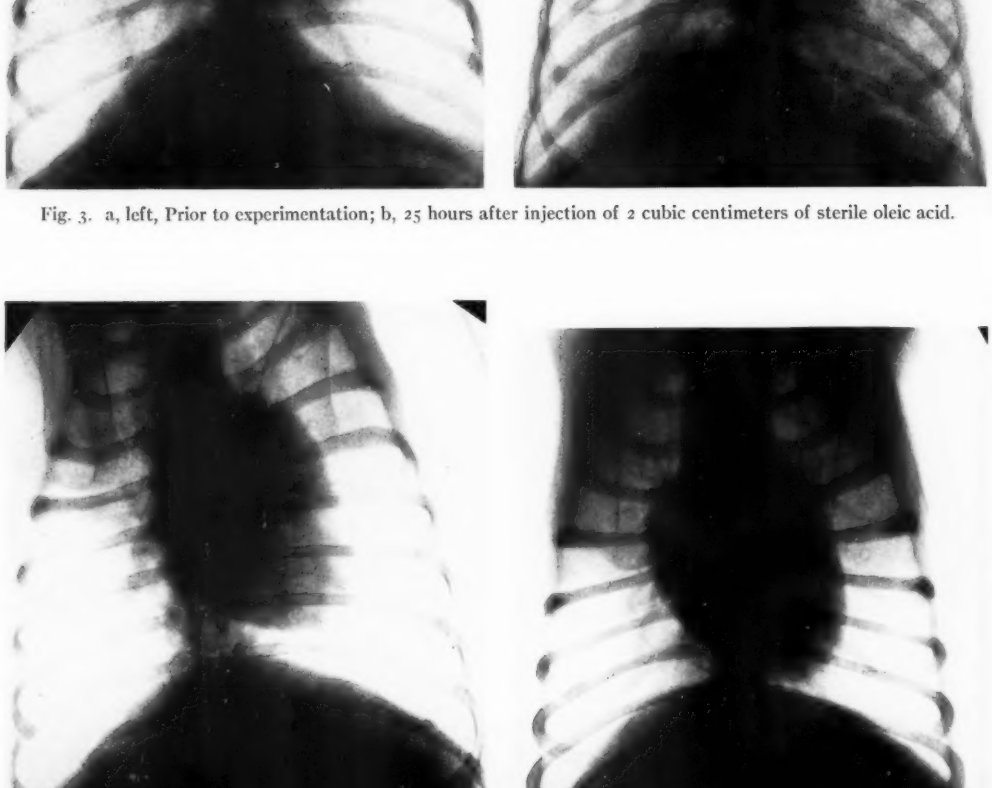


Fig. 4. a, left, Normal lung field; b, 48 hours after injection of 10 cubic centimeters of sterile olive oil.

FAT TOLERANCE IN DOGS— EXPERIMENTS IN IMMUNIZATION

That animals can be made tolerant to lethal doses of intravenous fat was first shown by Paul and Windholz in 1925. This was later confirmed by Domanig in 1932.

Paul and Windholz used repeated small doses of fat in daily injections. At each injection larger quantities were given. They at first thought that this increased tolerance was due to a greater production of serum lipase. However, careful investigation with the Traube stalagmometer failed to show any such rise. They then concluded that this increased tolerance was due to the acceleration of absorption of the fat by the tissues.

Domanig gave hourly injections of intravenous fat and was also able to create an apparent relative immunity to increasing doses of intravascular fat. He was unable to show any transferable fat dissolving or lipolytic substance created in these animals. He likewise concluded that the increasing doses created an accustomizing reaction of the body to the fat. By careful stool and urine examinations, he showed conclusively that there was no increased elimination which might explain the increased fat tolerance.

The above experimenters used small divided doses given at frequent intervals. The thought occurred to me to give massive sublethal doses with a longer interval between doses in the hope that by using this procedure perhaps the mechanism of fat tolerance might be different.

Paul and Windholz, and Domanig used both olive oil and human bone marrow fat. It appeared to me that if we expect any definite serological reaction, the bone marrow fat from dogs alone should be used in dogs. For this reason bone marrow fat obtained by extracting cut dog bones was used.

It was found that the minimal lethal dose was from 2.2 to 2.5 cubic centimeters per kilogram body weight of the animal.

By weekly injections of increasing doses 4 animals reached a figure of 5 cubic centimeters or more per kilogram body weight before the quantity of fat produced death. One animal received 5 cubic centimeters per kilogram, one 5.5 cubic centimeters; and 2 animals received 6 cubic centimeters per kilogram.

Three dogs were transfused with 65 to 85 cubic centimeters of citrated blood from the animals which had survived 5.5 cubic centimeters of bone marrow fat per kilogram of body weight.

In each instance after the termination of the transfusion, 3 cubic centimeters of dog bone marrow fat were injected per kilogram body weight (a lethal quantity). None of these animals survived. At least for the time being no transferable substance has been found which could be used to transmit a partial immunity or increased fat tolerance from one animal to another. Perhaps none exists and on the other hand perhaps other methods of approaching the problem may isolate it.

CONCLUSIONS

1. The literature shows conclusively that the postmortem table, unfortunately, is not the last court of appeal for fat embolism following fractures.

2. Quantitative blood fat determinations are of no value in the diagnosis, because the physiological variations are too great.

3. Qualitative dark field examinations of the blood should be of great aid in the diagnosis, in the hands of trained microscopists.

4. In the urine examination of suspected cases, only the last few cubic centimeters of a catheterized specimen are valuable.

5. Our uniformity of experimental results makes the author feel that intravenous fat droplets, if present in sufficient quantity, will always produce changes in the lung fields, detectable by the x-ray.

6. The sizzle test, using a platinum loop and a Bunsen burner, is accurate in 1:1400 to 1:1600 dilution. It is very simple and requires no special apparatus nor any complicated equipment.

7. The technique of Sudan III staining of the urine and blood specimens, in order to be accurate, must be done according to the following rules: (a) The stain must be fresh; (b) a high concentration of the dye is necessary to stain the fat droplets; (c) the stain must be permitted to act on the fat for at least 5 minutes in order to stain it well; (d) orange droplets less than 3 to 4 microns are either contamination or undissolved stain;

(e) a drop of stain must be added directly to the slide and not to a test tube specimen.

8. Gardinol and decholin sodium are of no value either as diagnostic or therapeutic drugs.

9. Fat droplets are excreted exclusively through the tubules of the kidney, if the concentration of the fat reaches 0.75 cubic centimeters or more per kilogram body weight.

10. Surface tension studies of the blood serum are of no value in this disease because the variables are too numerous to be satisfactorily controlled.

11. Since all the bone marrow fat extracted from a femur is not sufficient to cause death, the author believes, from experimental evidence, that oleic acid, which is one of the split products of the neutral olein of bone marrow, is the probable etiological factor. This substance is seven times as lethal as neutral bone marrow fat, and sufficient quantity could easily be available.

12. Experimentally, animals can be made resistant to lethal doses of intravascular fat provided the injections are given in gradually increasing doses. The mechanism of this phenomenon is not clear. Whether it is due to an increased tissue resistance or the formation of an emulsifying agent will require further work.

BIBLIOGRAPHY

1. Aberle, R. Ztschr. f. orthop. Chir.. 1907, 19:69–114.
2. Bantin, C. F. J. Am. M. Ass., 1926, 86:546–548.
3. Bang, I. Ztschr. f. Biochem., 1918, 91: 224.
4. Bissell, W. W. J. Am. M. Ass., 1916, 67: 1926.
5. Bloor, W. R. J. Biol. Chem., 1928, 77: 53–73.
6. Bloor, W. R., Pelkan, K. F., and Allen, D. M. J. Biol. Chem., 1922, 52: 191–205.
7. Buerger, L. Vrtljschr. f. gerichtl. Med. (supplement), 1910, 39: 159–172.
8. Caldwell, G. T., and Huber, H. L. Surg., Gynec. & Obst., 1917, 25: 650.
9. Carrara, M. Friedreich's Bl. f. gerichtl. Med., 1898, 49: 241–279.
10. Catsaras, J. Presse méd., 1920, 28: 618.
11. Cubbins, W. R. Personal communication.
12. Czerny, V. Berl. klin. Wchnschr., 1875, 12: 593–605.
13. Domanig, E. Deutsche Ztschr. f. Chir., 1932, 236: 693–703.
14. Edmunds, J. Monthly Micro. J., 1877, 18: 78–85.
15. Elting, A. W., and Martin, C. E. Ann. Surg., 1925, 82: 336–353.
16. Fritsche, E. Deutsche Ztschr. f. Chir., 1910, 107: 456–476.
17. Gage, S. H. Cornell Veterinarian, 1920, 10: 154–155.
18. Gage, S. H., and Fish, F. A. Am. J. Anat., 1924, 34: 1–25.
19. Gauss, H. Arch. Int. Med., 1916, 18: 76.
20. Idem. Arch. Surg., 1924, 9: 593–605.
21. Grondahl, N. D. Deutsche Ztschr. f. Chir., 1911, 111: 56–124.
22. Groskloss, H. Yale J. Biol. & Med., 1935–1936, 8: 59–91.
23. Jirka, F., and Scuderi, C. S. Arch. Surg., 1936 33: 708–713.
24. Kumagawa, M., and Suto, K. Ztschr. f. Biochem., 1908, 8: 212.
25. Landois, F. Deutsche med. Wchnschr., 1926, 52: 283–285.
26. LeCount, E. R., and Gauss, H. Tr. Chicago Path. Soc., 1915, 9: 251.
27. Lehman, E. P., and McNattin, R. F. Arch. Surg., 1928, 17: 179–189.
28. Lehman, E. P., and Moore, R. M. Arch. Surg., 1927, 14: 621–662.
29. Lexer, E. Lehrbuch der allgemeinen Chir., 3 auflage, 1908.
30. Lower. Quoted from Flournoy.
31. Magendie, F. Leçons sur les phénomènes phys. de la vie, 2, 1836.
32. Miloslavich, E. L. Wisconsin M. J., 1930, 29: 139.
33. Neumann, A. Zentralbl. f. Physiol., 1907, 21: 102.
34. Nicod, J. L. Schweiz. med. Wchnschr., 1938, 19: 845.
35. Paul, M., and Windholz, F. Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1925, 38: 614–651.
36. Rappert, E. Deutsche Ztschr. f. Chir., 1938, 250: 4.
37. Reiner, M. Muench. med. Wchnschr., 1907, 54: 2004–2005.
38. Riedel, B. Deutsche Ztschr. f. Chir., 1877, 8: 571.
39. Ryerson, E. W. J. Am. M. Ass., 1916, 67: 657.
40. Schanz, A. Zentralbl. f. Chir., 1916, 37: 43–44.
41. Scriba, J. Deutsche Ztschr. f. Chir., 1880, 12: 118.
42. Scuderi, C. S. Internat. Surg. Digest, 1934, 18: 195–215.
43. Idem. Arch. Path., 1939, 28: 668–675.
44. Simonds, J. P. J. Am. M. Ass., 1917, 69: 883.
45. Speed, K. Fractures and Dislocations. 1st ed. Lippincott, 1916.
46. Stoddard, J. L., and Drury, P. E. J. Biol. Chem., 1929, 84: 741–748.
47. Tanton, J. J. de chir., 1914, 12: 267–296.
48. Vance, B. M. Arch. Surg., 1931, 23: 426–465.
49. Warthin, A. S. Internat. Clin., 1913, 4: 171–227.
50. Wegelin, C. Schweiz. med. Wchnschr., 1923, 4: 133–138.
51. Wells, H. G. Quoted from Ryerson.
52. Wilms, M. Semaine méd., 1910, 30: 138–139.
53. Wright, R. B. Ann. Surg., 1932, 96: 75–84.
54. Zenker, P. A. Beitr. z. norm. u. path. Anat. d Lunge, 1862.

EXPERIENCES WITH INTRAMEDULLARY TRACTOTOMY

IV. Surgery of the Brain Stem and Its Operative Complications

FRANCIS C. GRANT, M.D., F.A.C.S., and LAURENCE M. WEINBERGER, M.D.,
Philadelphia, Pennsylvania

SURGICAL procedures upon the various extramedullary segments of the trigeminal nerve for the relief of major trigeminal neuralgia or for intractable facial pain due to other reasons have suffered from several drawbacks. All of these have not been eliminated by either the Frazier-Spiller retrogasserian neurotomy or by the Dandy-Olivecrona method of sectioning the trigeminal root in the posterior fossa. In both of these operations the resulting corneal insensitivity permits the occurrence of neuroparalytic keratitis. The face feels numb and stiff and roughly 5 per cent of patients develop distressing dysesthesias which often cause more suffering than did the original neuralgia.

To avoid these complications, Sjöqvist (6) in 1938 proposed cutting the descending tract of the trigeminal nerve within the medulla oblongata. The rationale for this new method was based on the peculiar anatomy of the intramedullary pathways of the trigeminal nerve. A brief and simple description of the central trigeminal fibers will provide the theoretical background of the operation.

The sensory root of the trigeminal nerve enters the brain stem at the junction of the pons and medulla. Immediately upon the entry the fibers undergo an anatomical separation and a physiological dissociation. The fibers mediating touch sensation turn rostrally and enter the main sensory nucleus of the trigeminal nerve and thence by the secondary neuron ascend to the sensory nucleus of the thalamus. The fibers mediating pain sensation, on the other hand, turn caudally and in company with the spinal nucleus of the trigeminal nerve run throughout the length of the medulla and into the upper cervical spinal cord. In the closed portion of the medulla they lie on the superficial lateral aspect where they form a distinct elevation, the tuberculum cinereum. The tuberculum cinereum is, in this situation, above the olivary eminence and below the restiform body. An incision into the tuberculum cinereum, therefore, cuts the descending tract of the trigeminal nerve and presumably avoids the important nuclei, tracts, and respiratory mechanisms in this neighborhood.

Since only the pain fibers are interrupted, certain advantages are apparent. Touch sensation is spared, and the face does not feel cold and numb. Neuroparalytic keratitis should not result since some sensation is retained in the eye. The motor component is also spared which makes the operation suitable for bilateral trigeminal neuralgia. Furthermore, Sjöqvist believed that facial dysesthesias would not follow this procedure.

Thirty-five operations of this type have been reported, of which 19 cases have been done in this clinic. Nine patients were originally operated upon by Sjöqvist (7), 3 cases have been reported by Rowbottom, 1 by Jackson and Ironside, 2 by Walker, and 1 by Smyth. The results in 19 cases in terms of relief of facial pain have been reported by Grant and Weinberger (3) as well as an analysis of the sensory phenomena (10), and neurologic sequelae (11).

SURGICAL TECHNIQUE AND PLACEMENT OF THE MEDULLARY INCISION

Before Sjöqvist performed this operation for the first time, it was thought extremely hazardous to incise the brain stem. As a matter of fact, it was believed that death could ensue if the medulla was accidentally penetrated during the performance of a cisternal puncture. From experiences with intramedullary tractotomy, it is now known that relatively large incisions may be made in the medulla with small risk to life, if carefully placed.

From the Neurosurgical Service and Neuropathological Laboratory of the Hospital of the University of Pennsylvania.

Anesthesia. The premedication used consists of 3 grains of nembutal given at midnight. The morning of operation, morphine sulphate, grains 1/6, and scopolamine, grains 1/150, are given 2½ hours before operation and again ½ hour before operation. In most instances avertin, 60 to 70 milligrams per kilogram, has been used as anesthetic, although in a few cases the premedication was so successful that it was possible to perform the operation with local infiltration of novocain into the scalp. There is an objection to local anesthesia because cutting the tract is painful and the patients move during the section. This can be dangerous since the movement may deflect the operator's hand while the knife blade is in the medulla.

Operative exposure. A conventional suboccipital hemicraniectomy is performed. It is not necessary to expose the lateral sinus. It adds to the ease of the subsequent manipulations to rongeur the bone a little past the midline. The entire posterior rim of the foramen magnum must be removed. This is especially important on the side of the projected incision since an adequate lateral view of the medulla is the *sine qua non* of the exposure. In taking away the most lateral bit of the foraminal rim, care must be taken not to injure the vertebral artery which enters the cranial cavity about a centimeter below. Although Sjöqvist, in his operative description, did not mention removing the arch of the atlas, we have found that a wider and better view of the medulla is secured by so doing. The dura is opened by radial incisions, and the flaps are tacked to the adjacent muscle. A linear incision is then extended downward to open the dura over the upper cervical cord. The arachnoid membrane of the cisterna magna is torn and the cerebrospinal fluid is allowed to escape. The medulla, with the emerging lower cranial nerve roots, comes into view. In most cases a large looping artery, the posterior inferior cerebellar, is seen lying against the side of the medulla just under the cerebellar tonsil. The cerebellar tonsil is gently retracted upward and rostrally by a small spatula protected with moist cotton. There are often small arachnoidal adhesions between the tonsil and the medulla, which may be gently separated without trouble. Occasionally these contain small veins which may be coagulated and cut. The tonsil is retracted until the obex of the fourth ventricle is visualized on the dorsal aspect of the medulla and the emerging rootlets of the ninth and tenth cranial nerves are seen on the lateral aspect (Fig. 1).

Placement of the incision and the anatomical problems involved. According to Sjöqvist the anatomical landmark selected to indicate the placement of the incision is the lowermost rootlet of the vagus nerve. At this level the point of the knife is inserted into the medulla just dorsal to the rootlet and carried dorsally for 4 millimeters. The depth of the incision is 3.5 to 4 millimeters. This incision severs the descending tract and spinal nucleus of the trigeminal nerve. However, if one studies a number of specimens of the medulla, one is struck by the variations in the number of vagal rootlets and their points of emergence from the medulla. It is this fact which most likely accounts for the several different and contradictory directions that Sjöqvist gives in his description of the site of the medullary incision. For instance, he writes (7, p. 98): "The incision is situated immediately caudal to the lowermost vagal filaments and a few millimeters dorsal to them. At this point the spinal tract is no more covered by the restiform body. The level corresponds to a border between the middle and inferior 2/3 of the eminentia olivaris. . . . This corresponds to a level 8 to 10 mm. cranially to the inferior end of the fourth ventricle."

On measuring out these distances on several specimens of the medulla, it was found that a distance of 8 to 10 millimeters above the obex actually corresponded to a level passing through the rostral tip of the olive or, in some cases, slightly above it. In a number of medullas the lowermost vagal rootlet was at the level of the midportion of the olive but never as far rostrally as 10 millimeters above the level of the obex. To add to the confusion, the author's drawing which illustrates the site of the incision shows it placed about 2 millimeters *above the highest vagal rootlet!* Furthermore, in case protocol 2 the incision was made, "10–12 mm. cranially to the inferior edge of the fourth ventricle." In Case 4 the incision

was made 8 millimeters above the level of the obex while in the 7 other cases it was variously described as being placed at the level of the middle or lower third of the olive or at the level of the lowest vagal rootlet. While Sjöqvist states that the restiform body is avoided by an incision at his recommended level (8 to 10 millimeters above the obex) the cross sectional view of the medulla in which he illustrates the extent of the proposed incision (7) shows the lower half of the restiform body included in the transection (Fig. 2a).

It is our belief, from experiences with the operation, that the placing of the incision 8 to 10 millimeters above the level of the obex will result in severe or disabling neurological sequelae in a high percentage of cases. These will come from injury to the restiform body or the main and/or lateral cuneate nuclei which are easily exposed to injury at this level. As in cordotomy, the site and extent of the operation must be measured in terms of millimeters and an error of a millimeter or so at this high level in the medulla may result in disastrous consequences. Although Sjöqvist denies that neurological complications occur, except for an occasional paralysis of the recurrent laryngeal nerve due to handling of the vagal rootlets, his case protocols offer evidence to the contrary. In Case 4 the patient following operation felt numbness in his contralateral extremities and in Case 9 the patient's gait was, "more markedly staggering than on admission." One also gets the impression that neurological compli-

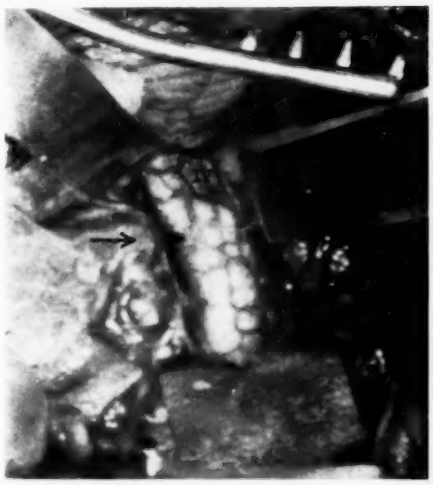


Fig. 1. Operative photograph of the medulla oblongata. The tonsil of the cerebellum is retracted to expose the lower portion of the fourth ventricle. The incision, which is marked by a black thread placed in it, is located at a level about 4 millimeters caudal to the obex. Only the dorsal half of the incision is seen; the lower half is concealed by the lateral curve of the medulla. This photograph was taken of Case 2.

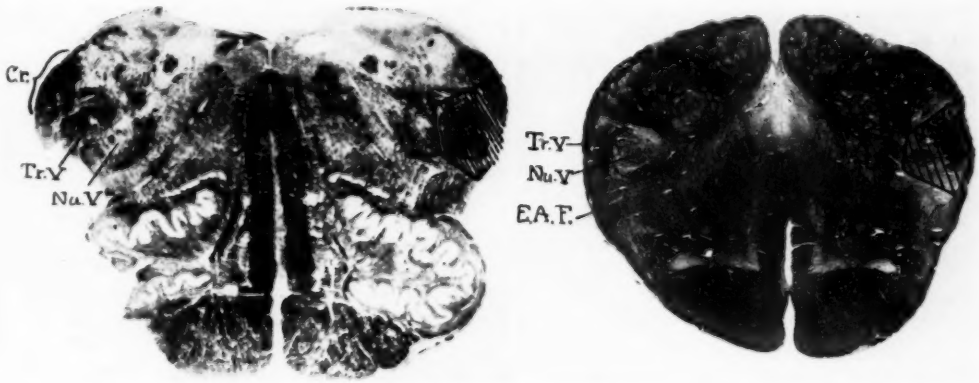


Fig. 2. a, left, reproduced from Sjöqvist's monograph (7, Fig. 32). The extent of the proposed incision indicated by the shaded area involves almost the lower half of the corpus restiforme, *C.r.* The cross section represents a level at about the middle of the fourth ventricle. b, is a cross section through the medulla taken 4 to 5 millimeters below the obex and about 2 millimeters caudal to the olive. The extent of the modified incision is shown by the shaded area. At this level the descending tract of the fifth nerve, *Tr.V*, is most superficial and covered only by a thin band of external arcuate fibers, *E.A.F.* The spinal nucleus of the fifth nerve, *Nu.V.*, is also fairly superficial.

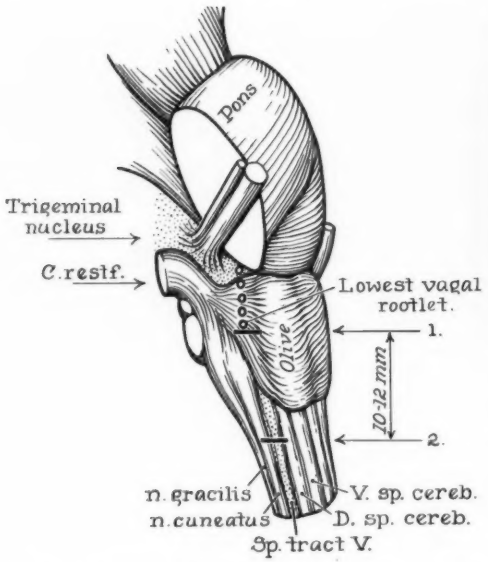


Fig. 3. Diagrammatic representation of the fiber tracts in the medulla. *1*, Indicates the site of the incision advocated by Sjöqvist. As shown it transects large bundles of fibers running to form the restiform body as well as the underlying cuneate nucleus. *2*, Indicates the site of the modified incision. In this latter place the incision only nicks a few of the dorsal column fibers and entirely avoids the restiform body. (Adapted from Figure 683, Gray's *Anatomy*, edited by Lewis, 1918. J. B. Lippincott Co.)

Fig. 4. Prepared specimen of the medulla oblongata. The stippled band outlines the medullary portion of the tuberculum cinereum which contains the descending tract and spinal nucleus of the trigeminal nerve. The *O* encircles the obex of the fourth ventricle which is the primary landmark for locating the medullary incision. Four to 5 millimeters caudal to it the incision is placed into the tuberculum cinereum as indicated by numeral *2*. The incision recommended by Sjöqvist is indicated by numeral *1*. This latter site almost inevitably involves the restiform body.

cations may not have occurred in other cases because the incision was not made deep enough to sever the descending tract. This is inferred because in Cases 6 and 7 no sensory alterations resulted in the face and in Cases 1, 2, 3, 5, and 8 complete analgesia was not produced in all three divisions but only in one or possibly two divisions. In 1 of Rowbottom's cases in which Sjöqvist's description was apparently followed, the author states that the patient had a "wild ataxia" of the arm following operation. In a case reported by Smyth and operated upon by Jackson the patient had postoperative incoordination of the arm and a staggering gait.

Since we have had mishaps of this nature, an attempt was made, based on a review of the known topographical anatomy of the medulla and the relationship of superficial to deep structures, so to modify the site of the incision as to render serious neurological complications unlikely and at the same time to secure an adequate facial analgesia. The following anatomical data are presented to explain the rationale of the modification.

The trigeminal nerve enters the lower portion of the pons and penetrates 4 or 5 millimeters until it reaches the lateral portion of the tegmentum. At this point 4 to 5 millimeters beneath the surface of the brain stem and under cover of the middle peduncle, it breaks up into the ascending fibers and into the descending fibers which form the descending tract. As the descending tract courses caudally it becomes more superficial and at the level of the middle of the fourth ventricle it is covered only by the restiform body on the dorsal and dorsolateral aspects. It is at this level that Sjöqvist recommends that the tract be sectioned. As the tract descends still more caudally it emerges from under the restiform body and at the level of the obex it is almost on the surface of the medulla and forms a well defined eminence, the tuberculum cinereum. Four to five millimeters below the level of the obex the restiform body is no longer present, and the tract is covered laterally by only the external arcuate fibers and the dorsospinocerebellar fibers. These run in a vertical ventrodorsal or in a vertically oblique direction so that the incision parallels their course (Fig. 3).

An incision into the medulla at this level cannot injure the restiform body or the cuneate nuclei and can only injure a few external arcuate and dorsal spinocerebellar fibers (Fig. 4). A transection at this level 3 to 4 millimeters deep will encompass all the fibers of the trigeminal tract and will assure an adequate facial analgesia (Fig. 2b).

It has been thought that only the fibers from the ophthalmic division descend to the cervical cord and that the fibers from the maxillary division end about the level of the lowest glossopharyngeal rootlets. The mandibular fibers were thought to terminate still higher in the medullary portion of the spinal nucleus (8). In 1 case in which we made the incision into the medulla about 8 millimeters below the level of the obex, a total and lasting analgesia was obtained in all three divisions of the face. This experience serves to prove that all divisions of the face are represented in the tract as low as the level of the upper pyramidal decussation. We feel, therefore, that it is safer to cut the medulla more caudally for the descending tract is most superficial and there are no vulnerable structures to be injured by an incision 3 to 4 millimeters deep.

When we first started to perform these operations 2 years ago, we used the level recommended by Sjöqvist (8 to 10 millimeters above the obex). Severe neurological symptoms followed operation which were first partly ignored since it was thought that they were only transitory. As the cases were followed over a period of many months it became evident that in a number of instances the disturbances persisted and produced considerable disability. It was this experience combined with the opportunity to study several postmortem specimens that caused us to modify the procedure. In order to illustrate the possibilities of injury to the restiform body and cuneate nuclei when making the high incision recommended by Sjöqvist, the following case is cited.

Case 1. R. J. Surgical 43547. The patient was a 46 year old male with carcinoma of the tongue and severe intractable pain in the left mandible. In order to relieve his pain it was thought necessary to render his face analgetic as well as to section the ninth nerve and the upper posterior cervical roots. On March 12, 1939, a suboccipital hemicraniectomy was performed, and the arch of the atlas was removed. The upper three cervical roots on the left side were cut and the glossopharyngeal nerve was sectioned. The tuberculum cinereum was then visualized by retracting the cerebellar tonsil. An incision was made into the tuberculum cinereum at a level 6 millimeters above the obex and approximately dorsal to the lowest vagal rootlet. The incision was 4 millimeters long and 3 to 4 millimeters deep.

Postoperative course: The patient was examined the day after operation. There was the anticipated analgesia involving all three divisions of the trigeminal territory. Touch sensation was grossly intact. The analgesia also involved the distribution of the upper three cervical roots. His pain had disappeared. However, there was a marked weakness of the homolateral arm and the patient complained of numbness and tingling in the fingers of the homolateral hand, i.e., homolateral to the side of the incision. There was a wild inco-ordination of the arm. The fingers were so clumsy that he could not hold or handle objects. Postural sensation was seriously impaired in the fingers of the left hand, less so at the wrist and slightly at the elbow. There were pseudoathetoid movements of the extended fingers. There was a mild inco-ordination of the left leg. Eight days later the inco-ordination of the arm was still marked though less than after operation. Postural sensation was still impaired in the hand and it still felt numb and tingling. He was unable to stand unsupported because of ataxia and staggering. He fell to the left. The difficulties in gait and equilibrium were disproportionate to the static cerebellar disturbances in the left leg. When discharged at the end of 2 weeks he was still too ataxic to walk unsupported and there was still inco-ordination in the arm and leg. Two months later and just before his death his wife wrote us that he could not walk because of staggering, that his left hand was still clumsy and that it felt numb.

Perhaps had he lived longer many of his neurological disabilities would have improved because our experience shows that this does occur. The operation, however, disabled him for 2 months. In this particular patient the neurological sequelae were a cheap price to pay for the relief of pain but this case emphasizes the serious complications that may occur with high placed incisions. Undoubtedly the restiform body and cuneate nuclei were injured. Although the neurological sequelae tend to disappear in time, 2 to 4 months' disability is a more serious consideration when dealing with cases of trigeminal neuralgia. Most of the patients operated upon in whom the Sjöqvist incision was used had considerable postoperative neurological disturbances. We have now performed 4 operations in which the incision was placed in the tuberculum cinereum 4 to 5 milli-

TABLE I.—SUMMARY OF DATA ON THE IMMEDIATE POSTOPERATIVE STATUS OF 19 CASES OF TRACTOTOMY

	Trigeminal neuralgia 7 cases	Malignant disease 12 cases
Complete relief of pain	7	9
Partial relief of pain	..	2
No relief of pain	..	1
Satisfactory facial analgesia	7	9
Unsatisfactory facial analgesia	..	3
Marked neurological disturbances	4	3
Moderate neurological disturbances	1	3*
Minor neurological disturbances	1	2
No neurological disturbances	1	1

*3 not known.

meters below the level of the obex. In comparison with the case described, we cite one such patient operated upon with the modification in the placement of the incision.

CASE 2. N. E. Surgical 36952. The patient was a 50 year old woman who had suffered with major trigeminal neuralgia, second and third divisions, for 2 years. She had received temporary relief from alcoholic injections but finally demanded permanent relief. An intramedullary tractotomy was performed April 24, 1940. The obex was used as the landmark and the tuberculum cinereum was transected at a level 4 to 5 millimeters below the obex and about 2 millimeters below the olive (Fig. 1).

Postoperative course: Six hours after operation the patient was clear and co-operative. Examination disclosed a slight inco-ordination of the homolateral arm. Her grip was good and there were no subjective sensations in the hand. Postural sensation was intact. By the end of 24 hours the inco-ordination had practically disappeared in the arm. There was a complete analgesia in all 3 divisions of the fifth nerve with gross preservation of touch sensation. When put on her feet on the third postoperative day she was unable to walk and fell promptly to the right side. Again the disturbances in equilibrium and gait were disproportionate to the static cerebellar signs for there was only the trace of a heel to knee ataxia when tested in bed. By the fifth postoperative day she was able to walk unsupported, although she frequently staggered to the right side. Her gait rapidly improved and by the twelfth postoperative day there was little evidence of disturbance. The Romberg sign was not present. There was no inco-ordination in either of the right extremities. One month after operation she was performing full household duties. Her only neurological complaint was a little insecurity in descending steps. Two months after examination she was examined and found to be neurologically normal. Her pain was entirely relieved and there was a complete analgesia of the three trigeminal divisions.

While mild neurological disturbances were present after operation, they were only transient and she left the hospital essentially a normal person. These transient symptoms were probably due to cutting of a few spinocerebellar and arcuate fibers and to the regional edema of the medulla. This case typifies the differences in the postoperative course when the incision is made low in the medulla as compared to the previous case in which it was made higher. Neurological compensation apparently is made readily after injuries to the spinocerebellar tracts and arcuate fibers whereas the defects are more profound and less recoverable when the restiform body or cuneate nuclei are injured. This has been shown experimentally in monkeys by Ferraro and Barrera.

TABLE II.—SUMMARY OF AVAILABLE FOLLOW-UP DATA ON 15 CASES OF TRACTOTOMY 1 TO 13 MONTHS POSTOPERATIVE

	Trigeminal neuralgia 6 cases	Malignant disease 9 cases	Not known
Complete relief of pain	4	5	
Partial relief of pain	1	3	
No relief of pain	1	1	
Satisfactory facial analgesia	4	3	4
Inadequate facial analgesia	2	2	
Marked neurological disturbances	1*	2	2
Moderate neurological disturbances	1	1	
Minor neurological disturbances	4		
No neurological disturbances		4	
Subjective facial sensations	3		5
No subjective facial sensations	3	4	

Average hospital stay, 14 days—Range 8—21.

*Underlying diffuse degenerative disease of C. N. S.

Before ending the section on the surgical and anatomical problems, brief mention should be made of several other difficulties encountered in the course of medullary surgery. Occasionally thick congeries of small vessels may be clustered over the area selected for the incision. This forces one to make the incision a millimeter or so away. We have adopted the policy of moving the incision caudally the required distance since the descending tract remains superficial throughout the lower medulla. It is unwise to coagulate these vessels on the medulla since the electric current is carried along the vessels into the brain stem and might produce serious results. If the incision is made into an avascular area, hemorrhage never occurs. Although Sjöqvist used a

straight blade to make the incision, we early found that it was difficult, if not impossible, to see the point of the blade enter the medulla. Using a curved blade No. 12 with a sharp point, one has a full view of the knife point and therefore better control over the length and depth of the incision. A bit of wax may be placed on the knife 4 millimeters above the point, to serve as a guard.

NONNEUROLOGICAL COMPLICATIONS

For 1 to 3 days after operation most patients have a marked headache due to blood in the posterior fossa, loss of cerebrospinal fluid, and air in the subarachnoid space. Five patients developed hiccoughs on the second to fifth day. These lasted 3 to 9 days and were refractory to all treatment although carbon dioxide inhalations gave temporary relief. In 2 instances they were very exhausting. No difficulties in swallowing or speech were encountered. In Sjöqvist's series there were 3 instances of recurrent laryngeal paralysis. We have not seen this complication. Although the medulla is necessarily incised in this operation we have not seen any respiratory difficulties on the operating table or thereafter.

MORBIDITY AND MORTALITY

The periods of postoperative hospitalization ranged from 8 to 21 days and averaged 14 days. Two patients with oral carcinoma died from late postoperative pneumonia on the thirteenth and seventeenth postoperative days. At necropsy, one patient showed a widespread pulmonary carcinomatosis and the other multiple pulmonary abscesses. One patient operated upon for a painful carcinoma of the cheek developed a postoperative psychosis which persisted and necessitated his removal to an institution.

SUMMARY AND CONCLUSIONS

The results of the operation in terms of relief of pain have been dealt with in other publications but are briefly summarized in Tables I and II.

Intramedullary tractotomy is neither a difficult nor a complicated operation but requires an intimate knowledge of the topographical and internal anatomy of the medulla oblongata. At present, the procedure is just moving out of the experimental stage. Similar hazards and complications were encountered in the early development of anterior cordotomy and it is expected that apprentice fees must be paid in order to develop, modify, and perfect the technique.

Although we do not, at present, feel that the operation is acceptable as a routine procedure in cases of trigeminal neuralgia, various conditions exist in which it might be considered the operation of choice. In cases of severe trigeminal neuralgia affecting the upper or upper two divisions or all three divisions of the face, tractotomy avoids the possibility of neuroparalytic keratitis which might result from the complete section of the root required to relieve the pain. In cases in which neuralgia has developed on the second side after a previous retrogasserian neurotomy has been performed, tractotomy avoids involvement of the motor component and preserves masseter function. In neurotic persons in whom one might expect severe distress from postoperative numbness if the sensory root were sectioned, tractotomy is indicated since there are fewer unpleasant subjective sensations in the face. Not infrequently careful questioning shows that a patient has a burning pain in the face between the paroxysms of true neuralgia. Our experience with such cases has taught us that this burning pain may persist in the anesthetic area and even be accentuated by the presence of the anesthesia. Medullary tractotomy relieves the paroxysmal pain without producing subjective sensory changes in the face. If the complete anesthesia produced by sensory root section could thus be avoided the burning paresthesia might be much less annoying. It has its widest application in cases of malignant disease about the head where pain makes it desirable to render the face analgetic. Since it is often necessary also to section the ninth nerve and posterior cervical roots, tractotomy can be easily done through the same exposure.

Most of the advantages claimed for the operation have been confirmed in our experience. Touch sensation for all practical purposes is preserved, and the patients are hardly aware that their faces have been made analgetic. No cases of neuroparalytic keratitis have been ob-

served nor have we even witnessed reddening of the conjunctiva. In the majority of cases, even with complete analgesia of the ophthalmic division, a blink reflex may be elicited. While pain sensation is lost in the cornea and the affective component of corneal irritation is absent, the patients are able to feel a stimulus on the cornea, the sensation being described as a light touch or tickle. Although it is too early to speak with assurance about postoperative dysesthesias, we have 4 patients with subjective facial sensations. In no case have they spontaneously complained of these sensations and in no instance have they been of the disagreeable or distressing character as are often a source of distress after sensory root section. One patient had slight burning sensations about the eye which were annoying but perfectly tolerable. One had prickling and tingling sensations for which he rubbed his face with liniment. One woman complained of brief paroxysms of burning at the angle of the mouth, and one stated that he had chilly sensations and the illusion that his nose was watering.

Theoretically, there is no reason why interruption of the intramedullary trigeminal pathways should not be followed by dysesthesias. It is well to recall in this connection, the fact that thromboses of the posterior inferior cerebellar artery which always involve the descending tract of the trigeminal nerve, are accompanied, in the majority of cases, by severe burning dysesthesias (12). Only a larger experience will determine whether they occur following surgical transection of the tract.

BIBLIOGRAPHY

1. Ferraro, A., and Barrera, S. E. The effects of lesions of the dorso-spinocerebellar tract and corpus restiforme in the macacus rhesus monkey. Brain, 1935, 58: 174.
2. Idem. Effect of lesions of the juxtarestiform body (I. A. K. bundle) in macacus rhesus monkeys. Arch. Neurol. & Psychiat., 1936, 35: 13.
3. Grant, F. C., and Weinberger, L. M. Experiences with intramedullary tractotomy. I. Summary of the operative results and complications. To be published.
4. Jackson, H., and Ironside, R. Left trigeminal pain treated by means of Sjöqvist's medullary trigeminal tractotomy. Proc. Roy. Soc. Med., 1939, 32, pt. 1: 219.
5. Rowbottom, G. F. Treatment of pain in the face by intramedullary tractotomy. Brit. M. J., 1938, 2: 1073.
6. Sjöqvist, Olaf. Eine neue Operations Methode bei Trigeminus Neuralgie. Durchschneidung des Tractus Spinalis Trigemini. Zentralbl. Neurochir., 1938, 2: 274.
7. Idem. Studies on pain conduction in the trigeminal nerve. A contribution to the surgical treatment of facial pain. Suppl. 17. Acta psychiat. et neurol. 1938.
8. Smyth, G. E. The systemization and central connections of the spinal tract and nucleus of the trigeminal nerve. Brain, 1939, 62: 41.
9. Walker, E. A. Anatomy, physiology and surgical considerations of the spinal tract of the trigeminal nerve. J. Neuropathy, 1939, 2: 234.
10. Weinberger, L. M., and Grant, F. C. Experiences with intramedullary tractotomy. II. Studies in sensation. In preparation for publication.
11. Idem. Experiences with intramedullary tractotomy III. The immediate and late neurologic disturbances. In preparation for publication.
12. Winther, Knud. Tractotomy (Sjöqvist) viewed in the light of the pathology of the medulla oblongata. Acta psychiat. et neurol., 1939, 14: 243.

EXPERIMENTAL CEREBRAL TRAUMA

II.—Further Observations on the Fluid Content of the Brain Following Trauma to the Head

COBB PILCHER, M.D., F.A.C.S., Nashville, Tennessee

IN experiments previously reported (2), it was found that there was little, if any, significant alteration of the fluid content of various parts of the dog's brain after trauma to the head sufficiently severe to produce a marked rise in cerebrospinal fluid pressure. Since, theoretically, with skull and dura mater intact, an increase in tissue fluid volume could occur only at the expense of a diminution in intracranial blood or cerebrospinal fluid volume, similar experiments have been made with one hemisphere of the brain freely exposed. These experiments offer the additional advantage of comparison of the exposed with the unexposed hemisphere, as well as with normal control values.

METHODS

Anesthesia, position of the head, and methods of sacrifice of the animals and isolation of specimens of cerebral gray and white matter, cerebellar gray matter and brain stem are exactly as described in the previous study (2). Specimens of cerebral gray and white matter were removed from both hemispheres in all experiments. Fluid content was determined by drying to constant weight at 60 degrees C. as before. Trauma was administered by dropping a 1000 gram weight from a distance of 60 inches twice in rapid succession. This degree of trauma has been found to produce consistently a marked elevation in cerebrospinal fluid pressure when skull and dura are intact. Cerebrospinal fluid pressure and femoral arterial pressure were determined as in the preceding study.

Two types of experiments were performed. In the first type, the entire left cerebral hemisphere was exposed, the dura being incised in stellate fashion and its flaps laid back. The exposed brain was lightly covered with a flat sheet of warm, moist cotton which was moistened from time to time with warm physiological saline solution. No trauma was administered. After intervals of from 4 hours to 5¼ hours, specimens were rapidly removed for determination of fluid content. Seven such experiments were performed.

In the second type of experiment, trauma was administered as described and the left hemisphere was exposed immediately afterward. The animals were sacrificed and specimens were secured 4 hours after trauma in 2 experiments, 4½ hours after trauma in 2 experiments, and 8 hours after trauma in 2 experiments. No visible hemorrhage was present in any experiment.

From the Department of Surgery, Vanderbilt University School of Medicine.

RESULTS

Left hemisphere exposed. No trauma. The arterial blood pressure was not significantly altered during any experiment. The cerebrospinal fluid pressure was very slightly elevated in one animal (Dog T 67) and elevated 185 millimeters of water above the control level in another (Dog T 68). In the latter the cotton pad over the left hemisphere was adherent to the brain at the end of the experiment. When it was gently removed, a gush of fluid followed and the cerebrospinal fluid pressure fell to the control level. In the remaining experiments, the cerebrospinal fluid pressure was not altered. Bulging of the exposed hemisphere at the end of the experiments was absent in 5 dogs, slight in 1 dog, and marked in 1 dog.

The fluid content of the brain specimens is given in Table I. Although there were occasional individual variations, the findings, for the most part, were surprisingly uniform as was found in the previous study. No significant difference could be demonstrated between the fluid contents of corresponding specimens

TABLE I.—LEFT HEMISPHERE EXPOSED—NO TRAUMA

Dog number	Left cerebral gray matter—percentage of fluids	Left cerebral white matter—percentage of fluids	Right cerebral gray matter—percentage of fluids	Right cerebral white matter—percentage of fluids	Cerebellar gray matter—percentage of fluids	Brain stem—percentage of fluids	Time hrs.
T 62	76.6	69.0	78.0	70.0	79.4	70.5	4¼
T 63	78.6	65.6	77.5	71.0	79.2	69.7	4
T 64	80.5	72.2	81.3	71.3	80.5	72.5	4¼
T 65	79.6	72.1	81.1	70.0	80.6	72.7	4
T 67	77.7	66.4	76.7	61.4	79.5	69.5	4
T 68	79.1	68.6	80.6	68.8	80.0	71.5	4½
T 69	81.0	66.8	81.3	67.0	80.2	70.0	5¼
Average	79.0	68.6	79.5	68.5	79.9	70.9	

TABLE II.—TRAUMA—LEFT HEMISPHERE EXPOSED

Dog number	Left cerebral gray matter—percentage of fluids	Left cerebral white matter—percentage of fluids	Right cerebral gray matter—percentage of fluids	Right cerebral white matter—percentage of fluids	Cerebellar gray matter—percentage of fluids	Brain stem—percentage of fluids	Time hrs.
T 70	78.1	67.8	79.8	67.0	79.3	70.8	4½
T 71	81.0	69.3	78.8	69.8	81.2	72.0	8
T 72	78.9	65.7	78.6	64.7	78.9	69.3	8
T 73	78.7	66.3	78.8	66.0	79.6	68.2	4
T 74	79.4	67.2	79.3	66.7	79.7	70.9	4½
T 75	80.0	66.6	79.6	66.5	79.8	71.5	4
Average	79.3	67.1	79.1	66.8	79.7	70.4	

from the left and right hemispheres. Average findings were almost identical in the two hemispheres and they also corresponded very closely with the findings in normal control animals, as will be pointed out later.

Left hemisphere exposed. Severe trauma. The arterial blood pressure showed a transitory fall followed by a slight elevation immediately following trauma. Otherwise it was not significantly altered. The cerebrospinal fluid pressure was not measurably elevated during any of the experiments, doubtless due to the open wound through which fluid could freely pass. The exposed left hemisphere bulged moderately in 4 experiments and not at all in 1. In the single remaining experiment (Dog T 70), the brain was actually shrunken and retracted from the dura by the end of the experiment. In this animal, the respirations rose from a control rate of 30 to 80 per minute 1 hour after trauma, then slowly fell to, and remained at, 40. The dog was moderately cyanotic, but the arterial blood pressure maintained a constant normal level.

The fluid contents of the specimens from the dogs' brains are shown in Table II. The uniformity of the various values is even more striking than in the untraumatized animals. In every experiment, there were almost identical values for corresponding specimens from the two hemispheres, and the average findings are virtually the same as normal control values (see below).

For purposes of comparison, a composite table of averages is presented in Table III. The extremely close correspondence of values for the respective specimens in the different groups of experiments is self-evident.

SUMMARY AND CONCLUSION

In an excellent study of traumatized human brains, Shapiro and Jackson have found actually subnormal values for the water content of traumatized brains. Using the iron determination method, they also have shown that the

TABLE III.—COMPOSITE TABLE OF AVERAGES

Type of experiment	Number of experiments	Left cerebral gray matter—percentage of fluids	Left cerebral white matter—percentage of fluids	Right cerebral gray matter—percentage of fluids	Right cerebral white matter—percentage of fluids	Cerebellar gray matter—percentage of fluids	Brain stem—Percentage of fluids
1. Normal controls*	5	79.4	68.0			79.6	70.9
2. Trauma, no operation	15	79.9	68.9			79.7	71.1
3. Left hemisphere exposed, no trauma	7	79.0	68.6	79.5	68.5	79.9	70.9
4. Left hemisphere exposed—trauma	6	79.3	67.1	79.1	66.8	79.7	70.4

*Experiments reported in preceding paper (2).

intracerebral blood volume, whether intravascular or extravascular, is greater than normal in such brains (Pilcher, 2). They state, "In the traumatized head the brain is accordingly swollen but not edematous; the swelling is not due to increased water but to increased blood content."

Alexander and Looney studied the brains of a series of patients who died in a psychiatric hospital. They concluded that the water content of the brain is not "positively correlated with edema or atrophy of the brain." It is apparent that the contradiction between these two quotations is one of terminology and not of fact. The *American Illustrated Medical Dictionary* defines "edema" as "swelling due to an effusion of water liquid into the connective tissue," but Alexander and Looney apparently employ the term to describe brains the size of which is greater than normal. They state, "Atrophy or edema of the brain can be measured quantitatively only by the differential ratio of skull capacity to brain volume or brain weight." The findings of Alexander and Looney do not offer proof of the existence of "cerebral edema," within the meaning of the definition quoted.

The experiments reported in this paper clearly demonstrate the marked stability of the fluid content of brain tissue. Under these experimental conditions, no significant change in fluid content has been produced.

REFERENCES

1. Alexander, L., and Looney, J. M. Physicochemical properties of brain, especially in senile dementia and cerebral edema. Differential ratio of skull capacity to volume, specific weight, water content, water-binding capacity and p^H of the brain. Arch. Neurol. & Psychiat., 1938, 40: 877.
2. Pilcher, C. Experimental cerebral trauma. The fluid content of the brain after trauma to the head. Arch. Surg., 1937, 35: 512.
3. Shapiro, P., and Jackson, H. Swelling of the brain in cases of head injury. Arch. Surg., 1939, 38: 443.

PLASMA PROTHROMBIN VALUES OF MOTHERS AND INFANTS AT DELIVERY

Further Studies Including Comparative Values of the Umbilical Arteries and Veins

ROBERT F. NORRIS, M.D., and MATTHEW C. BENNETT, M.D.,
Philadelphia, Pennsylvania

THE widespread interest in prothrombin and vitamin K deficiencies has been responsible for several studies on the relationship of these deficiencies to the hemorrhagic diseases of the newborn. The simple clinical method of Quick, Stanley-Brown, and Bancroft (16, 17) or one of its modifications (11, 12, 13), and the more complicated two-stage titration method of Warner, Brinkhous, and Smith (19, 23) have been the favorite procedures for the estimation of prothrombin deficiency and therefore indirectly in certain instances of the vitamin K deficiency. At the time of birth, by the Warner method, the blood prothrombin has been shown by Brinkhous, Smith, and Warner (4), by Owen, Hoffman, Ziffren, and Smith (9), and by Hellman and Shettles (5) to be only about one-quarter that of the normal adult. By the Quick method, however, this deficiency is not so apparent since an increase in the convertibility of prothrombin into thrombin may compensate in part for the deficiency of the former (9). With their method Quick and Grossman (14, 15) found, however, that the prothrombin values of the newborn varied between 60 and 70 per cent of normal.

The available evidence also indicates that in many infants a marked fall in the level of prothrombin may occur 2 or 3 days after birth (9, 14, 15, 20, 21). A gradual rise in the prothrombin level during the next week normally occurs, but this change may be accelerated by the oral administration of vitamin K (18). It is during these first days of life, therefore, when the plasma prothrombin is low that hemorrhage is apt to occur.

From the Ayer Clinical Laboratory and the Obstetric Service (Philadelphia Lying-In) of the Pennsylvania Hospital.

Employing the method of Warner, Brinkhous, and Smith (19, 23), Hellman and Shettles (5) were the first to compare the prothrombin levels of mother and infant. They found that the concentration of prothrombin in normal full term infants averaged less than one-quarter that in the mothers. Norris and Rush, using the Quick method, found that in the case of 50 mothers and their babies the average level of the babies was 63 per cent of the normal controls and that of the mothers 140 per cent when 25 per cent diluted plasmas were compared as against 85 per cent and 117 per cent, respectively, when undiluted plasmas were compared.

Hellman and Shettles (5) likewise noted that the level of plasma prothrombin tended to be even lower in immature infants than in full term babies. Kato and Poncher (7), however, found no correlation between the infant's maturity and the prothrombin level of the blood as measured by the microprothrombin method of Kato (6). When the prothrombin level by this method was determined on successive days following birth a greater fluctuation of the values was observed in the blood of the premature than in the mature infants.

The cause of the low prothrombin content in the cord blood of the fetus and the apparent fall in the plasma prothrombin level of many infants after birth has not been determined. Norris and Rush suggested that since the prothrombin concentration of mothers at delivery averaged above normal a deficiency of maternal vitamin K probably is not responsible for the low prothrombin of the fetuses. Since the rôle of the liver in elaborating prothrombin from vitamin K has been established

in experimental animals (2, 14, 15, 19, 22, 23), it has been assumed that the liver of the fetus and newborn is likewise responsible for the formation of prothrombin (14, 15). During intra-uterine life, therefore, vitamin K must be supplied to the fetal liver by way of the mother, but after delivery this source of supply is abruptly removed. Quick (14, 15), therefore, believed that this sudden removal of vitamin K is responsible for the fall of plasma prothrombin during the first days of life. Since Almquist and Stokstad have shown that in the intestinal tract of chicks bacteria may synthesize vitamin K, Quick (14, 15) suggested that when the bacterial flora of the infant's intestinal tract is established vitamin K may be produced by bacterial activity in the intestines. The time when vitamin K thus becomes available corresponds to the time when a rise of the prothrombin level normally occurs.

Because of these uncertainties it was thought important to study a large series of cases in order to determine whether any relationship exists between the prothrombin levels of individual mothers and babies. It also seemed advisable to ascertain whether the prothrombin levels of umbilical arteries and veins are identical in individual cases.

METHODS

In the comparison of the individual maternal and infant prothrombin levels, 35 additional cases were added to the original 50 cases of Norris and Rush. All prothrombin values were determined by the method of Quick (16, 17). In the 35 new cases the plasma prothrombin was determined not only in the umbilical vein but also in the umbilical artery. For this purpose blood was collected by the method of Boyd and Wilson. At the time of delivery the umbilical cord was sectioned without clamping 10 to 12 centimeters from the fetus. Blood which ran freely from the placental end of the cord was assumed to be largely from the umbilical vein and blood which spurted from the fetal end was assumed to be from the umbilical artery. Collected simultaneously in separate paraffin-lined beakers, the specimens were immediately mixed in test tubes with the appropriate amounts of sodium oxalate solution. Blood was also collected at once by venipuncture from the mother. In the preparation of the solution of thromboplastin we have followed Quick's modification (11, 12, 13) of his original method in regard to heating the saline mixture and the omission of the oxalate solution from the saline preparation of rabbit brain, but we have continued to use normal hospital workers as controls on each day that determinations were made instead of using Quick's formula for computing the prothrombin values of unknown plasmas. Our experience has been in agreement with Pohle and Stewart's in that the 0.025 molar calcium chloride solution used by Quick often gives slower clotting times than solutions of lower concentration. Consequently, in the last 17 cases we have employed 0.005 molar calcium chloride solution for all determinations. Although the speed of clotting with this concentration is increased the relation between unknown and control appear to be maintained in the same proportion. In all cases we have compared not only the undiluted plasmas of the unknown with the dilution values of the control, but we have also compared the 25 per cent diluted plasmas of each. For interpolation of these dilutions and for the evaluation of an unknown undiluted plasma which clots faster than the control, we have used the formulas of Norris and Rush. In 22 of the last 35 cases the volume of packed erythrocytes in the blood of umbilical artery and vein was also measured.

RESULTS AND COMMENTS

The prothrombin values of 35 additional mothers and babies at delivery were averaged with the 50 mothers and 51 babies (including one pair of identical twins) previously reported by Norris and Rush. Prothrombin determinations on blood from only the umbilical veins of the babies were included in the series. In Table I the average prothrombin value of undiluted maternal blood plasma is seen to be 111 per cent and that of the fetal blood to be 77 per cent of normal. The average prothrombin value, when the plasmas diluted to 25 per cent are compared, is seen to be 136 per cent and 64 per cent, respectively. In the first 50 cases reported a tendency for dilution of the plasmas to increase the value

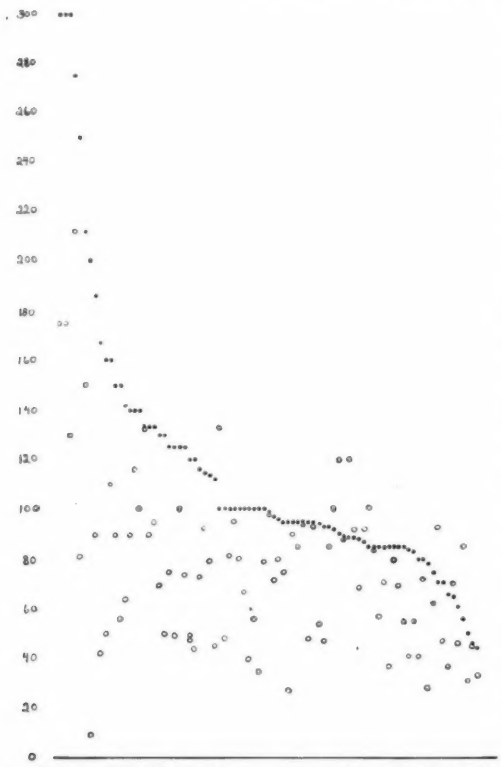


Chart 1. Undiluted plasmas. Comparison of individual prothrombin values in percentage of normal in 85 mothers and their babies. Solid dots are maternal values, circles are fetal values.

of prothrombin in the case of the mothers and to diminish it in the case of the babies as compared to the normal controls was also observed. The explanation for this difference is not apparent, but it has been suggested that dilution of the plasmas may increase the accuracy of the test (8, 9, 14, 15). At any rate the low prothrombin level of infants at birth does not appear to be caused by vitamin K deficiency in the mothers.

It is of interest that so many of the maternal plasmas appeared to have higher than normal prothrombin values. In the case of the undiluted plasmas 31 were greater than the respective controls and in the 25 per cent diluted plasmas 65 of the 85 maternal plasmas were greater than the controls.

Little has been said in the literature of the possibility that certain individuals may have greater than normal prothrombin values. Pohle and Stewart have found that with the Quick test normal plasma will clot in 10 seconds in the presence of an optimal calcium concentration, but this time is the minimum unless the plasma is grossly lipemic when slightly faster times may be obtained. Such findings imply, at any rate, that if clotting is faster than normal the increased speed is not due to more than a normal amount of prothrombin. Even by varying the amount of added calcium in an effort to find the optimal concentration, as suggested by Pohle and Stewart, we have been unable to obtain for normals minimum clotting time approaching 10 seconds. The clotting time for normal undiluted plasmas, depending upon the solution of thromboplastin used, varies between 12 and 14 seconds in our hands. In a number of cases in which the clotting time of the mother's plasma was faster than that of the normal control, varying the calcium concentration did not reduce the clotting time of the normal to that of the mother's plasma. None of these plasmas, furthermore, was lipemic. It appears to us, therefore, that if the increased speed of clotting of many of the maternal plasmas is not due to increased amounts of prothrombin the factors responsible for this phenomenon are as yet undetermined.

TABLE I.—A COMPARISON OF THE SPREAD OF THE PROTHROMBIN VALUES FOR MATERNAL AND VENOUS CORD BLOOD OF 85 MOTHERS AND 86 BABIES IN PERCENTAGE OF NORMAL

	100% Plasma		25% Plasma	
	I. Maternal blood %	II. Venous blood %	I. Maternal blood %	II. Venous blood %
Maximum.....	300	212	270	108
Minimum.....	44	9	64	9
Mean.....	111	77	136	64

TABLE II.—A COMPARISON OF THE SPREAD OF THE PROTHROMBIN VALUES FOR ARTERIAL AND VENOUS CORD BLOOD OF 35 BABIES IN PERCENTAGE OF NORMAL

	100% Plasma		25% Plasma	
	I. Arterial blood %	II. Venous blood %	I. Arterial blood %	II. Venous blood %
Maximum.....	100	120	92	96
Minimum.....	7	9	7	9
Mean.....	60	66	54	65

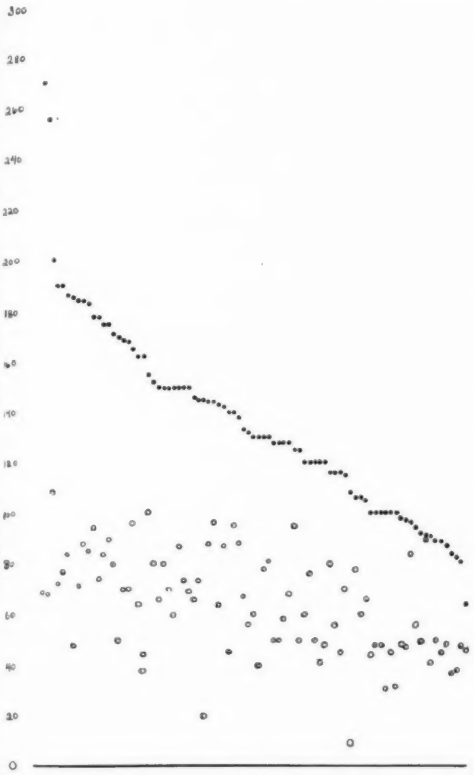


Chart 2. Twenty-five per cent diluted plasmas. Comparison of individual prothrombin values in percentage of normal in 85 mothers and their babies. Solid dots are maternal values, circles are fetal values.

In Charts 1 and 2 the individual prothrombin values of mothers and babies at delivery in percentage of normal are compared. Chart 1 is a comparison of the undiluted plasmas and Chart 2 of the 25 per cent dilutions. The solid dots are the maternal prothrombin values, arranged in diminishing order of percentage, and the circles are the prothrombin values of blood from the umbilical veins of the respective infants. From these charts it is quite apparent that there is no correlation between the amount of the plasma prothrombin of individual mothers and babies. In the case of the undiluted plasmas in Chart 1 some of the infants even have higher values than their mothers. In Chart 2 none of the infant prothrombin values exceed their mothers' prob-

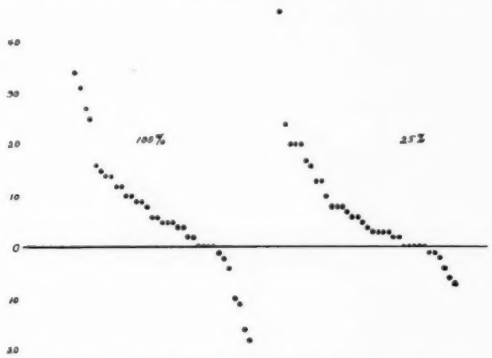


Chart 3. Percentage differences of prothrombin values between individual umbilical arteries and veins in the case of undiluted and 25 per cent diluted plasmas. Above the zero line are those cases in which the value of the vein exceeded the artery, below the line those in which the artery exceeded the vein, and on the line those in which the artery and vein were equal. Thirty-five cases.

ably because of the tendency of dilution to increase the spread in the prothrombin levels of mothers and babies. It may be concluded, therefore, that the amount of plasma prothrombin in the infant at delivery is not directly dependent on the amount of maternal prothrombin.

The prothrombin values in blood from the umbilical artery and vein were compared in the 35 additional cases which we are reporting. In Table II it will be seen that the mean prothrombin value of blood from the umbilical veins exceeds that of the umbilical arteries by 6 per cent in the undiluted plasmas and by 11 per cent in the 25 per cent diluted plasmas. In Chart 3 the differences in veins and arteries of the 35 cases are plotted. Above zero are plotted the differences in percentage of those cases in which the plasma prothrombin is greater in the vein than in the artery and below zero those cases in which the value of the artery is greater than in the vein. On the zero line are those cases in which the plasma prothrombin is identical in artery and vein. It will be seen that in 24 of the 35 cases the value for the vein exceeds the artery. Although these cases are too few and the spread of values is too great for statistical analysis, especially when it is possible that the Quick test is not accurately quantitative, the number of cases in which the plasma prothrombin is higher in

the vein than in the artery is great enough to indicate that similar results might be obtained in a large series of cases. If it is assumed, therefore, for purposes of discussion that these results are not due solely to chance and are a definite indication of differences in the artery and vein, several possible explanations should be considered.

The first possibility is that absorption of fluid from the fetal circulation through the placenta into the maternal circulation might increase the concentration of prothrombin in the plasma of the umbilical vein. In 22 of the 35 cases the volume of packed erythrocytes was measured. In 3 cases the volumes were identical. In 10 cases the volume was greater in the artery than in the vein and in 9 cases the volume was greater in the vein than in the artery. The usual variation was not greater than 1 per cent. Hemoconcentration, therefore, is not a significant factor in increasing the concentration of prothrombin in the umbilical veins.

It may be that factors other than prothrombin which influence the speed of clotting are responsible for the apparent differences in the prothrombin values of arteries and veins. Pohle and Stewart have shown that changes in the calcium concentration affect the speed of clotting and there is reason to suppose that changes in the concentration of other electrolytes might have a similar effect. We have no data in the present study on differences in the electrolytes of the umbilical artery and vein. As already indicated Pohle and Stewart found that lipemia will increase the speed of clotting. This observation may have a bearing on the present study since Boyd and Wilson reported that blood in the umbilical vein has a higher lipoid content than blood in the umbilical artery. Although determinations of fats and lipoids have not been made in these cases, it may be pointed out that in no instance was the plasma from the umbilical vein grossly lipemic.

In spite of these possible explanations, however, the increase in the amount of prothrombin in the umbilical vein may be not only apparent but also real. No one has suggested that prothrombin itself will pass directly from the maternal into the fetal circulation and the lack of any relationship between the amount of maternal and fetal prothrombin indicates that diffusion from mother to child is unlikely. If such diffusion does not occur, therefore, it is possible that prothrombin may actually be formed by the placenta during the period of gestation and the fall in the prothrombin level of some infants following birth may be due in part to the removal of such a source of supply.

SUMMARY AND CONCLUSIONS

1. By the Quick method the average plasma prothrombin value of 85 mothers at delivery was greater than the normal controls. The average value of their infants was less than the normal controls.

2. No relationship between the level of prothrombin in mother and baby could be demonstrated. It is unlikely, therefore, that prothrombin passes directly from mother to fetus.

3. A comparison of the plasma prothrombin levels of the umbilical artery and vein in 35 cases showed that in approximately 70 per cent of these cases the prothrombin value of the vein exceeded that of the artery.

4. If this apparent difference between artery and vein is a real one it is possible that prothrombin may be formed by the placenta.

The authors are indebted to Drs. Norris W. Vaux, Clifford B. Lull, and Robert A. Kimbrough, Jr., for permission to use their cases, and to Miss Marian M. Janney for her technical assistance.

BIBLIOGRAPHY

1. Almquist, H. J., and Stokstad, E. L. R. J. Nutrition, 1936, 12: 329.
2. Andrus, W. DeW., Lord, J. W., Jr., and Moore, R. A. Surgery, 1939, 6: 899.
3. Boyd, E. M., and Wilson, K. M. J. Clin. Invest., 1935, 14: 7.
4. Brinkhous, K. M., Smith, H. P., and Warner, E. D. Am. J. M. Sc., 1937, 193: 475.
5. Hellman, L. M., and Shettles, L. B. Bull. Johns Hopkins Hosp., 1939, 65: 138.
6. Kato, K. Am. J. Clin. Path., 1940, 10: 147.
7. Kato, K., and Poncher, H. G. J. Am. M. Ass., 1940, 114: 749.
8. Norris, R. F., and Rush, A. Surg., Gynec. & Obst., 1940, 70: 1006.
9. Owen, C. H., Hoffman, G. R., Ziffren, S. E., and Smith, H. P. Proc. Soc. Exper. Biol. & Med., 1939, 41: 181.
10. Pohle, F. J., and Stewart, J. K. Am. J. M. Sc., 1939, 198: 622.
11. Quick, A. J. J. Am. M. Ass., 1938, 110: 1658.

12. Idem. Pennsylvania M. J., 1939, 43: 125.
13. Idem. Proc. Soc. Exper. Biol. & Med., 1939, 42: 789.
14. QUICK, A. J., and GROSSMAN, A. M. Proc. Soc. Exper. Biol. & Med., 1939, 41: 227.
15. Idem. Am. J. M. Sc., 1940, 199: 1.
16. QUICK, A. J., STANLEY-BROWN, M., and BANCROFT, F. W. J. Biol. Chem., 1935, 109: p. lxxiii.
17. Idem. Am. J. M. Sc., 1935, 190: 501.
18. SHETTLES, L. B., DELFS, E., and HELLMAN, L. M. Bull. Johns Hopkins Hosp., 1939, 65: 419.
19. SMITH, H. P., WARNER, E. D., and BRINKHOUS, K. M. J. Exper. Med., 1937, 66: 801.
20. WADDELL, W. W., JR., and GUERRY, DUP., III. J. Am. M. Ass., 1939, 112: 2259.
21. WADDELL, W. W., JR., GUERRY, DUP., III, BRAY, W. E., and KELLY, O. R. Proc. Soc. Exper. Biol. & Med., 1939, 40: 432.
22. WARNER, E. D. J. Exper. Med., 1938, 68: 831.
23. WARNER, E. D., BRINKHOUS, K. M., and SMITH, H. P. Am. J. Physiol., 1936, 114: 667.

RESULTS OF PLASTIC OPERATIONS ON THE RENAL PELVIS AND URETER

ABRAHAM HYMAN, M.D., F.A.C.S., and SEYMOUR F. WILHELM, M.D., F.A.C.S.,
New York, New York

THE answer to the question, "Are plastic operations on the renal pelvis and ureter justified?," can be found only in a careful analysis of single case reports with postoperative pyelographic follow-up. The authors, therefore, have studied individually the 32 plastic operations performed at the Mt. Sinai and the Beth Israel Hospitals during the past 13 years. Most of these patients were operated on by the authors, several by the late Dr. Edwin Beer, and a few cases by other staff surgeons.

There were 5 operations of necessity, the ureter being reimplanted during pyelolithotomy. These cases have been reported in detail elsewhere (7). There were 2 failures. In 1, the anastomosis did not heal. The ureter separated from the pelvis and the kidney was subsequently excised. In the second unsuccessful reimplantation, the anastomosis healed well. However, the stoma was somewhat narrowed and the kidney, which had been grossly infected at the time of operation, gradually became functionless.

These 5 patients, operated on by 5 different surgeons, constitute a special group. In all the kidney was the seat of a calculus with severe infection. The pelvis and ureter were markedly inflamed, and their friability was in every instance considered by the operator the predisposing cause of the avulsion. In 2 of the cases, however, the immediate cause was undue traction on a loop around the ureter. The infiltrated condition of the tissues, as well as the irregularity of the tear, made accurate approximation impossible. Despite these difficulties, good functional results were observed shortly after operation and at later pyelographic examinations in 3 of the 5 cases of ureteral avulsion.

The 27 remaining plastic operations were done for hydronephrosis caused by obstruction at the ureteropelvic junction. There were 3 patients in whom a plastic was performed on a solitary kidney. One patient, suffering from bilateral obstruction, had both sides operated on.

Relief of the obstruction was the primary object of the surgical treatment in all cases. In 12 instances, the cause of the blockage was extrinsic, that is, due to vessels, bands, or adhesions, arising from outside the urinary passages. In 13 cases, the obstruction was due to intrinsic lesions, such as stricture or abnormal insertion of the ureter. In the 2 remaining cases, a portion of the redundant pelvis was resected following pyelolithotomy. The authors have excluded from this study all cases of hydronephrosis due to extrinsic obstruction or to calculus, unless a plastic operation on the renal pelvis or ureter was also done.

A dilated kidney and pelvis often will return to relatively normal size if the obstruction is relieved at an early stage. This is especially true in calculous cases in which the obstruction is frequently quite sudden. On the other hand, in some of the larger and more chronic hydronephroses, it was deemed necessary, in addition to relieving the obstruction, also to reduce the size of the redundant pelvis by resection or plication.

Simple resection. Resection of the dilated pelvis was the sole plastic procedure in 13 cases. The ureteropelvic obstruction had been adequately relieved by division of aberrant vessels or adhesions, or in 2 instances by pyelolithotomy (Table 1). One patient died of accidental mercury poisoning 18 days after operation. This curiously was the only death in the 32 plastic operations. The obstruction was unrelieved in only 1 of the 10 cases in which patients returned to follow-up; nephrectomy was done. The 9 other patients were followed from 5½ months to 12 years; they were well with good renal function. All but one were controlled by excretory or retrograde pyelography, and frequently by both.

One of these cases illustrates the value of preliminary nephrostomy drainage in the treatment of grossly infected obstructive hydronephroses.

CASE 16. Beth Israel Hospital No. 81,402. This 34 year old man was admitted to the hospital with severe pain in the left loin and high temperature due to a purulent hydronephrosis (Fig. 1). A nephrostomy was performed without mobilization of the kidney. The patient's condition improved and 3 weeks later the kidney was exposed and mobilized. The pelvis was still greatly dilated, and there were large aberrant vessels with fibrous bands running over and constricting the ureteropelvic junction. The

From the Urological Surgical Services of the Beth Israel and Mt. Sinai Hospitals.

vessels and bands were divided. The pelvis was opened, a calculus was removed, and an oval flap from the redundant posterior pelvic wall was excised. A nephrostomy tube was reinserted and a second splinting catheter was placed in the ureter and brought out through the cortex adjacent to the nephrostomy. An excretory urogram (Fig. 2), made 3 years after operation, showed excellent function and a much smaller pelvis on the side operated on.

Pelvic plication. In 1 case (Beth Israel Hospital No. 104,488) the dilated pelvis was plicated after the obstruction had been adequately relieved by the freeing of ureteropelvic adhesions. A nephropexy was done. A good anatomical and functional result was seen on the excretory urogram 1½ years later.

The pelvis was plicated in 2 other cases, one (Case 31) in association with a side-to-side anastomosis, and the other (Case 27) in addition to section and reimplantation of the ureter. The end result in both of these cases was good. Pelvic plication seems to add little to the risk of operation.

Plastics at the ureteropelvic junction. The obstruction was intrinsic in 13 cases, having been caused either by stricture or by abnormal insertion of the ureter. These cases presented a more difficult surgical problem and were treated by a variety of plastic procedures. They are classified under the following headings: (a) Fenger pyeloplasty (2), Y-plastic (3, 11); (b) section of the ureter with reimplantation into the most dependent portion of the pelvis (8, 9); (c) lateral anastomosis of the ureter to the lowermost portion of the pelvis (1).

Fenger pyeloplasty. Three Fenger pyeloplasties were done, all before 1932. One patient (Mt. Sinai Hospital No. 299,803) was unrelieved and came to nephrectomy 4 years after operation. The second patient (Beth Israel Hospital No. 37,399) suffered several attacks of acute pyelonephritis and later developed a large perinephric abscess which was drained. Subsequently he passed a small calculus. Despite these complications, however, an excretory urogram made almost 3 years after operation showed good function and a smaller pelvis (Figs. 3 and 4). The third case (Mt. Sinai Hospital No. 344,622) also developed perinephritis, but 4 years later showed good function on excretory urography. He still complained of occasional loin pain.

Y-plastic. Two Y-plastic operations were done. In the first case (Beth Israel Hospital No. 105,877) there was little, if any, improvement in renal function despite a satisfactory anatomical result. The parenchyma had obviously been irremediably damaged by long standing obstruction and infection. A conservative plastic operation was attempted in this case only because the function of the other kidney had also been impaired by adhesions causing ureteropelvic obstruction.[1] In the second case (Beth Israel Hospital No. 116,482) an excretory urogram, made 7 months after operation showed excellent renal function and a small pelvis.[2]

TABLE 1—Results

Avulsion of ureter	Cases	Followed	Successful	Failed	Deaths
Reimplantation	5	5	3	2	0
Hydronephrosis: Plastic operations					
Simple resection	13	11	9	1	1
Simple plication	1	1	1	0	0
Fenger	3	3	2	1	0
Y-plastic	3	2	1	1	0
Section, reimplantation	6	6	4	2	0
Lateral anastomosis	2	2	2	0	0
	27	25	19	5	1

Results. The published results of the Fenger operations have been, for the most part, poor (4, 5). Animal experiments indicate that the obstruction is often unrelieved due to buckling of the posterior ureteral wall opposite the plastic suture line. On the other hand, the satisfactory anatomical and functional results in 2 of our cases proves that this is not a constant occurrence. In both of these cases, however, the patients were later operated on for perinephritis. It is interesting to speculate whether the failure to provide free urinary drainage by nephrostomy may have contributed to the high incidence of postoperative perinephric infection.

The Y-plastic, a modification designed to overcome the objections to the Fenger pyeloplasty, resulted in an apparently adequate stoma in our 2 cases. The functional result in one was poor, however, the parenchyma having been irremediably damaged.

Section and reimplantation of the ureter. The authors have observed 6 cases in which the ureter was completely severed and then reimplanted into the dependent portion of the pelvis. These cases were followed for a period of from 1½ to 7½ years after operation. There were 2 failures; one ended in nephrectomy, and the other, a case of giant hydronephrosis in a solitary kidney, was living 4 years later with a permanent nephrostomy. The result in each of the following 4 cases was fairly satisfactory.

CASE 26. Mt. Sinai Hospital No. 344,467. This 52 year old woman entered the hospital with high temperature due to a solitary infected hydronephrotic left kidney (Fig. 5). A right nephrectomy had been done for hydronephrosis in 1909. At operation (Dr. Edwin Beer) on October 22, 1932, the left ureter was found stenosed just below its junction with the pelvis. The pelvis was distended with frank pus.

[1] A secondary nephrectomy was recently done at another hospital.

[2] A plain film and excretory urograms made on December 2, 1940, revealed recurrent calculi with considerable hydronephrosis.

The stricture was resected and the cut end of the ureter was reimplanted into the pelvis over a splinting ureteral catheter. A portion of the redundant pelvis was then excised, the opening sutured, and a nephrostomy made.

The patient had a prolonged and stormy convalescence, marked by septic temperature with repeated chills. Colon bacilli were recovered in the blood culture. The bacteremia was gradually overcome, the patient making a slow recovery and leaving the hospital 2½ months after operation. She has lived fairly comfortably and has attended to her household duties for over 7 years, suffering occasionally from attacks of chills and fever. A retrograde pyelogram (Fig. 6), made in August, 1939, showed considerable dilatation of the pelvis and ureter. She was well when last seen by Dr. W. Menscher early in 1940.

CASE 25. Beth Israel Hospital No. 69,995. This case was reported in some detail (10). At operation on January 8, 1935, the left renal pelvis was found to be very large and distended with straw-colored fluid. The entrance of the ureter into the pelvis was markedly constricted. The ureter was divided below the stricture, and reinserted into the most dependent portion of the pelvis through a new opening. The ureter was sutured to the pelvis with fine plain catgut sutures over a Garceau catheter, which was brought out through the renal cortex and lumbar wound. The upper end of the ureter was split into 2 flaps which were sutured to the inner surface of the pelvis. A nephrostomy was also made, using a Pezzer catheter.

The immediate postoperative result was good. Indigo carmine appeared from the left pelvis in 5 minutes in good concentration. Excretory and retrograde pyelograms showed, however, some tendency to narrowing at the ureteropelvic junction. The latest excretory urogram, made on March 2, 1939, showed a mild degree of hydronephrosis with clubbing of the calyces and diminished function. Early in 1940, the patient, refusing further x-ray study, stated that she was well.

CASE 27. Beth Israel Hospital No. 106,124. An 8 year old boy was admitted to the hospital with pus and blood in the urine. Pyelography revealed a right hydronephrosis with trapping at the ureteropelvic junction. At operation, on November 3, 1938, the pelvis was considerably dilated and there was marked stenosis of the upper 2 centimeters of the ureter. The stenosed area was resected. The transversely cut end of the ureter was reimplanted into the pelvis over a splinting No. 5 French ureteral catheter, which was brought out through the lower pole next to a nephrostomy catheter. The redundant pelvis was closed by plicating sutures.

The immediate postoperative course was uneventful. However, when the splinting catheter was removed on the twentieth postoperative day, the stoma did not function. A retrograde pyelogram, made through the nephrostomy, revealed complete obstruction at the ureteropelvic junction. A cystoscope was then introduced into the pelvis through the nephrostomy sinus, but attempts to dilate the stoma from the pelvis downward were unsuccessful. Two days later, however, a catheter was easily passed from below up the right ureter into the pelvis. The stoma was then dilated on several occasions with indwelling ureteral catheters. The wound healed promptly, following removal of the nephrostomy tube on the thirty-sixth postoperative day. This boy has now been perfectly well for about 1¼ years after operation. The latest excretory urogram, made on March 14, 1940, showed good function and no progression of the hydronephrosis. The urine was clear.

CASE 28. Mt. Sinai Hospital No. 290,099. This case has recently been reported in detail (6). At operation on September 20, 1932, the left kidney and pelvis were found greatly dilated, and the upper inch of the ureter was markedly stenosed. The lower portion of the pelvis with the attached stenosed ureter was resected. The pelvis was closed with fine catgut and a No. 8 French soft catheter was inserted through the cortex into the pelvis and ureter, as a splint. The ureter was reimplanted into the pelvis.

On the eighteenth postoperative day, the tube was pulled upward out of the ureter into the pelvis. Indigo carmine, injected through the nephrostomy tube, did not appear in the bladder. On the other hand, a catheter was easily passed from below through the anastomotic stoma into the pelvis. It was evident that the anastomosis was obstructed only to the downward passage of fluid. This was repeatedly confirmed by clamping the nephrostomy tube and injecting indigo carmine. Despite several transcystoscopic dilatations, the efferent function of the stoma could not be established.

Three months after operation, a cystoscope was introduced through the nephrostomy sinus into the renal pelvis. A sickle-shaped fold of mucosa, noted just below the ureteropelvic junction, was thought to be the possible cause of the obstruction. This valve-like fold was electrocoagulated, and a No. 5 French ureteral catheter was passed from below into the pelvis and out through the nephrostomy sinus. The nephrostomy tube was reinserted. Following several transcystoscopic dilatations, the nephrostomy tube was again clamped off. The stoma was now functioning well. The nephrostomy tube was finally removed 5 months after operation, and the wound was dry within 24 hours.

This patient has been followed for 7 years. During this time, she re-entered the hospital on 6 occasions for cardiovascular disease and increasing hypertension. In 1937, a splanchnic sympathectomy, celiac ganglionectomy, lumbar ramisectomy, and hemi-adrenalectomy were done on the right side. There was no lasting improvement. She was admitted to the Montefiore Hospital in 1939 for hypertension, and an excretory urogram showed good function of both kidneys. There were no renal symptoms.

Renal function after operation was fairly good in 4 of the 6 cases of section and reimplantation of the ureter. One of these (Case 26), a woman with an acutely infected solitary hydronephrotic kidney, was living comfortably 7½ years after operation. Another (Case 25), followed 4 years, shows some narrowing of the stoma with a gradual decline in renal function. Although ultimately satisfactory, the 2 remaining cases developed complete obstruction to the downward flow of urine at the site of anastomosis immediately after removal of the splinting catheter. Pyeloscopy through the nephrostomy sinus in Case 28 revealed a valve-like mucosal fold, which was thought to be the cause of the obstruction. Following electrocoagulation of this fold and transcystoscopic dilatation from below, the patency of the stoma was permanently re-established. The function of this kidney was still fairly good 7 years after operation.

In Case 27, the postoperative obstruction of the stoma was overcome by repeated transcystoscopic dilatation from below. Renal function was good 1½ years later.

Unrelieved obstruction and infection were responsible for both failures. The first (Case 29.

Fig. 1. Case 16. Retrograde pyelogram which was taken before operation.

Fig. 2. Case 16. Excretory urogram 3 years after operation.

Fig. 3. Case 21. Excretory urogram which was taken before operation.

Fig. 4. Case 21. Excretory urogram 3 years after Fenger pyeloplasty.

Fig. 5. Case 26. Excretory urogram before operation in solitary kidney.

Fig. 6. Case 26. Retrograde pyelo-ureterogram made 7¾ years after section and reimplantation of ureter in solitary kidney.

Mt. Sinai Hospital No. 372,441) was a solitary infected giant hydronephrosis due to stricture. The ureter was sectioned and reimplanted but the new stoma failed to function well. This patient was alive almost 4 years later with a permanent nephrostomy. The second unsuccessful case (Case 30. Mt. Sinai Hospital No. 415,327), a 12 year old boy, left the hospital, presumably well, with a healed wound 22 days after operation. Two weeks later, the kidney became quite tender and the temperature rose to 104 degrees. The lumbar wound opened spontaneously, draining purulent urine. Nephrectomy was done.

The chief difficulty in the cases of section and reimplantation of the ureter was early postoperative obstruction at the site of anastomosis. This occurred in 4 of the 6 cases. Fortunately, however, the obstruction was successfully relieved in 2 cases, in one by electrocoagulation of a mucosal valve, followed by transcystoscopic dilatation, and in the other by dilatation alone. It seems apparent that an effort should be made at the time of operation to prevent the formation of a ureteral fold or cuff at the site of anastomosis. When possible, the ureter should be split for a distance of about a centimeter into 2 straps (Fig. 7). These are then fastened to the inner aspect of the pelvis by interrupted fine plain catgut sutures. Accurate apposition at suture line is obviously essential. More complicated techniques (10) have been suggested, but are rarely practical.

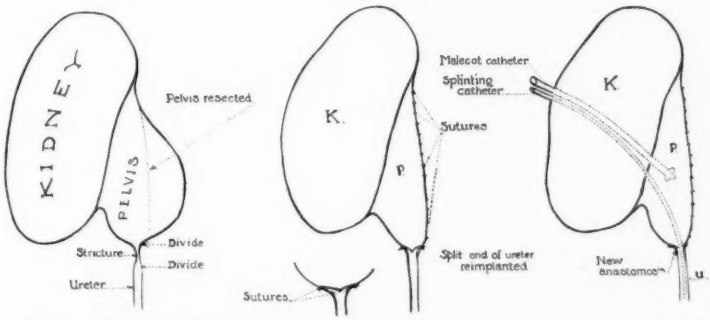


Fig. 7. Diagram illustrating section and reimplantation of ureter and resection of pelvis.

Lateral anastomosis. In 2 cases, a side-to-side anastomosis was made between the upper ureter and the most dependent portion of the pelvis. When technically feasible, such a lateral anastomosis has the following advantages over section and reimplantation (13): (1) The vascular supply of the upper ureter is preserved by leaving the ureter attached to the pelvis; (2) there is less interference with peristalsis; (3) a side-to-side anastomotic stoma can be made much larger, thereby lessening the likelihood of early or late stricture.

CASE 31. Beth Israel Hospital No. 75,048. This case has been previously reported in detail (13). At operation on June 20, 1935, the right kidney was greatly dilated. The ureter had a high anterolateral insertion with definite narrowing. A veil of fibrous adhesions extended over the ureteropelvic junction, causing an angulation at the point of insertion of the ureter. A side-to-side anastomosis was made, over a splinting No. 14 French rubber catheter. A nephrostomy was also done. The redundant pelvis was plicated, following scarification of its external wall. The postoperative course was uneventful, the nephrostomy tube was removed on tenth postoperative day and splinting catheter on sixteenth postoperative day. Patient has been observed for 5 years with repeated excretory and retrograde pyelograms. Renal function is good, patient is well.

CASE 32. Beth Israel Hospital No. 94,935 (12). This 31 year old man complained of dull pain in the right loin for 10 months and of severe pain the left loin for 4 days. An excretory urogram revealed a large hydronephrosis on the left side and no visualization on the right (Fig. 8). A retrograde pyelogram (Fig. 9) revealed a huge functionless sac replacing the right kidney. At operation on August 2, 1937, a large left hydronephrosis was found. The ureter had a high lateral insertion, forming an obstructive angle. A side-to-side anastomosis was made over a splinting No. 8 French ureteral catheter, the catheter being brought out through the cortex. A nephrostomy and nephropexy were also done. The splinting catheter was removed on the twelfth postoperative day. On September 16, 1937, a right nephrectomy was performed. The left nephrostomy tube fell out on September 22, and the wound healed. The patient left the hospital on October 18, voiding well.

Fig. 8. Case 32. Pre-operative excretory urogram showing a left hydronephrosis and absent function on the right.

Fig. 9. Case 32. Pre-operative right retrograde pyelogram.

Fig. 10. Excretory urogram made 2½ years after side-to-side anastomosis. Solitary kidney. Patient well.

He was readmitted 24 hours later with severe pain in the left loin, high fever, and anuria. At cystoscopy, the bladder was empty and an impassible obstruction was encountered in the left ureter 4 centimeters above its orifice. A nephrostomy was immediately performed and a week later the patient was again able to void. This obstructive episode was probably due to a small non-opaque calculus, which, however, was not recovered. The ureteropelvic stoma was dilated a number of times from below. The nephrostomy tube was then clamped off and the patient voided normally. A clamped-off nephrostomy tube was left *in situ* as a safety valve for about a year. The tube was finally removed and the wound healed promptly. The urine cultures at various times had shown Bacillus coli, Bacillus pyocyaneus, and Bacillus lactis aerogenes. After course of sulfanilamide, urine became sterile. Blood non-protein nitrogen was 38 milligrams. An excretory urogram, June, 1940 (Fig. 10), showed good function of left kidney. Patient well and working 3 years after operation.

The end-result in the 2 cases of lateral anastomosis was satisfactory. In Case 31, in which a pelvic plication was also done, the function of the kidney operated on was good after 5 years. In the second case, the anastomosis was made on a solitary kidney. This patient is well with adequate renal function 3 years after operation.

ANALYSIS OF STUDY

Increased experience with plastic operations on the renal pelvis and ureter has established the following principles: (1) Free urinary drainage by means of nephrostomy; (2) splinting of anastomosed parts by means of a catheter; (3) accurate apposition of sutured parts.

Nephrostomy. Free drainage is a prime requisite in the treatment of urinary infection from which most of these patients suffer. A nephrostomy should, therefore, be performed in all cases in which any extensive pelvic or ureteropelvic plastic procedure is done. The tube acts as a safety valve, preventing undue internal tension on the suture lines. In addition, it may be used for the instillation of bactericidal solution.

Prolonged drainage is often desirable. The anastomosis is put to a practical functional test by clamping off the nephrostomy tube for several days before its final removal. Should the anastomosis fail to function satisfactorily, the tube is again allowed to drain. This gives additional opportunity for edema and infection to subside and for transcystoscopic dilatation of the stoma. In 2 cases (Cases 27 and 28), a cystoscope was introduced through the nephrostomy sinus for direct visualization of the pelvis and site of anastomosis. In one of these, endopelvic electrocoagulation of a valve-like mucosal fold was followed by the permanent re-establishment of patency of the stoma.

The authors believe that the nephrostomy tube should be left in place for at least 2 weeks and often for a much longer time. It should be removed only after the adequacy of the anastomotic opening has been proved and when the infection has been well controlled. The administration of drugs, such as sulfanilamide and sulfapyridine is frequently effective, especially after removal of the tube.

The splinting catheter. A straight ureteral catheter is inserted into the ureter for a distance of about 10 centimeters below the site of anastomosis and brought out through the renal pelvis and cortex. It serves the double purpose of immobilizing the anastomosed parts and maintaining the new opening. The splinting catheter should be left in place for at least 10 days since its early removal may result in stricture or occlusion of the stoma.

Accurate apposition. Accurate suture of the mucosa and the muscularis in separate layers is recommended when possible, by means of fine interrupted plain catgut sutures for the mucosa and fine interrupted chromic sutures for the outer layers. Non-absorbable suture materials are contra-indicated since they act as foreign bodies and

may precipitate calculous formation when in contact with urine.

SUMMARY

1. The results of 32 plastic operations on the renal pelvis and ureter have been reported and analyzed. In 5 cases, the ureter was reimplanted in the renal pelvis following accidental avulsion. The 27 remaining plastic operations were done for hydronephrosis due to obstruction at the ureteropelvic junction.

2. Relief of obstruction was the primary object of the surgical treatment of hydronephrosis. In some cases, the dilated pelvis was also resected or plicated.

3. The various types of plastic operations employed are discussed and evaluated, and illustrative cases are recorded in some detail.

4. Early postoperative obstruction at the site of anastomosis was encountered in 4 of 6 cases of section and reimplantation, and in 2 of 5 cases of reimplantation following accidental avulsion.

5. Transcystoscopic dilatation was effective in several cases in overcoming early postoperative obstruction.

6. Direct pyeloscopy through the nephrostomy sinus was done in 2 cases. In 1 instance, the patency of the stoma was re-established, following electrocoagulation of a valve-like mucosal fold near the site of anastomosis.

7. Late stricture was observed in 1 case of section and reimplantation, 1 case of reimplantation following avulsion, and 1 case of Fenger pyeloplasty.

8. Side-to-side anastomosis of the ureter and pelvis, when feasible, appears preferable to section and reimplantation.

REFERENCES

1. ALBARRAN, J. Médecine opératoire des voies urinaires. Pp. 222–226. Paris: Masson, 1909.
2. FENGER, C. J. Am. M. Ass., 1894, 22: 335, 840.
3. FOLEY, F. E. B. J. Urol., 1935, 34: 612.
4. HENLINE, R. B. J. Urol., 1935, 34: 584.
5. HERBST, R. H., and POLKEY, H. J. J. Urol., 1930, 23: 23.
6. HYMAN, A., and LEITER, H. J. Mt. Sinai Hosp. In press.
7. HYMAN, A., and WILHELM, S. F. J. Urol., 1940, 43: 52.
8. KUESTER, E. Die Chirurgie der Nieren. Pp. 503–508. Stuttgart: Ferd. Enke, 1896–1902.
9. Idem. Arch. f. klin. Chir., 1892, 44: 850.
10. LUBASH, S. J. Urol., 1935, 34: 222.
11. SCHWYZER, A. Schweiz. med. Wchschr., 1931, 12: 1185.
12. WILHELM, S. F. Discussion American Urological Association, Buffalo, 1940. J. Urol. In press.
13. WILHELM, S. F., and BLINICK, G. Am. J. Surg., 1937, 35: 90.

USE OF THE LAG SCREW FOR INTERNAL FIXATION OF INTERTROCHANTERIC FRACTURES OF THE FEMUR

MELVIN A. CASBERG, M.D., St. Louis, Missouri

FROM the standpoint of medical literature one is impressed by the obscurity into which extracapsular fractures of the femur have fallen. Recent progress in the therapy of intracapsular fractures has so absorbed medical interests that there is a tendency to neglect an adjacent fracture of equal importance. Prior to Smith-Petersen's contribution to the therapy of fractures of the femoral neck, the capsule played an important rôle as a landmark of prognostic value. This factor was first emphasized by Sir Astley Cooper, who distinguished between intracapsular and extracapsular fractures and defined the poor prognosis of the former and the much better prognosis of the latter. True as these facts are they have in many instances led to a certain therapeutic fallacy in the assumption that treatment of extracapsular fractures is relatively unimportant because union is inevitable. Though this assumed truism is correct in part it is better clarified by the additional statement that union is inevitable in those patients who survive a sufficient period of time to permit such a process!

The study of mortality statistics in intertrochanteric fractures is rather disturbing and is prone to produce a somewhat pessimistic attitude. In the St. Louis City Hospital during 1937 the mortality rate for extracapsular fractures was approximately 40 per cent, while for intracapsular fractures it was 28 per cent (9). This difference is made possible by two definite factors: first, intertrochanteric fractures in general are associated with more shock and with greater trauma to the soft tissues as well as to the bone; second, the age of those suffering extracapsular fractures averages from 3 to 10 years above that of those with fractures of the femoral neck (11, 12). Intertrochanteric fractures usually show considerable trauma of the vastus lateralis, rectus femoris, and tensor fascia lata muscles with the extravasation of blood into the muscle bodies and even the presence of large intramuscular hematomas. This excessive tissue damage is the exception in fractures of the femoral neck where the trauma is localized fairly well within the joint capsule.

In recapitulation it might be stated briefly that to a certain extent the therapeutic problem presented by intracapsular fractures is that of union, whereas, in extracapsular fractures the problem of union is secondary to that of the maintenance of life.

In 1871 Hodgen described a swinging double inclined plane splint that is still employed by some surgeons in the therapy of extracapsular fractures. Though this method of treatment has produced excellent anatomical results in our hands, it requires the patient to remain in bed during the

From the Department of Surgery, St. Louis City Hospital.

a b c d

Fig. 1. a, Roentgenogram taken on admission of W. W. (Case 1), male, aged 52 years. Routine operation was performed. Complete reduction and fixation are shown in b and c. Patient was permitted to be up in a wheel chair on twelfth day, walked with the aid of crutches on the eighteenth day, and bore weight, still with the aid of crutches, 5 weeks after operation. Eight weeks after operation the crutches were discarded and the patient walked using a cane. d, taken 3 months after operation shows the amount of callus covering the tail of the screw. Patient followed for 10 months and has free motion of involved hip. (Operation August, 1939).

interim of immobilization, which averages about 10 weeks. This prolonged period of recumbency is a dangerous factor, especially in the aged. Various methods of fixation have been devised in order to permit the patient greater mobility. One of the better known is the well leg traction splint described by Roger Anderson. With this type of fixation the patient may be permitted a certain degree of mobilization almost immediately following reduction. Utilization of this principle in the St. Louis City Hospital (14) during the year 1938 to 1939 improved the mortality statistics slightly more than 10 per cent. Though there are certain disadvantages, the chief of which is the difficulty in rehabilitation due to pain in the joints, well-leg traction affords good fixation for a large percentage of intertrochanteric and subtrochanteric fractures.

Key, in an effort to reduce the high mortality rate in trochanteric fractures of the femur, resorted to internal fixation of these by the insertion of the Smith-Petersen nail. This method did not prove entirely satisfactory, for Key states, "In the beginning we had hoped for a method which would fix these trochanteric fractures to the same degree and afford the same freedom from casts and splints and permit the patient to be gotten out of bed soon after the operation, as is the case in fractures through the neck of the femur which have been nailed. However, it seems evident that this is not possible, because of the tendency to comminution and of the rather wide variation in the type of fracture encountered."

Fig. 2. Photograph (Case 1) taken 3 weeks after operation to demonstrate free motion of the hip.

THE LAG SCREW

It is not the purpose of this paper to discuss the advantages or disadvantages of the flanged nail, pin, or screws in the fixation of femoral neck fractures, for, in the hands of their individual masters each has proved successful. It is the purpose of this paper, however, to discuss the Leydig and Brookes (10) modification of the Henderson lag screw as a method of fixation of certain selected intertrochanteric fractures. This lag screw cannot be used indiscriminately on all extracapsular fractures and the cases must be selected carefully from the standpoint of the type of fracture. Subtrochanteric and markedly comminuted intertrochanteric fractures do not lend themselves to this type of fixation, for it is essential to have a

a b c

Fig. 3. a, Roentgenogram taken on admission of M. S. (Case 2), female, aged 69 years. b and c were taken immediately after operation. The patient was up in a wheel chair on the fourth day, and was walking with the aid of crutches just 2 weeks after operation. Weight bearing was commenced 5 weeks after operation and the crutches were discarded 5 weeks later, though at times one crutch was used when the patient had to walk more than usual. Motion at the hip was free and painless. Five months after operation the patient was using a cane but was able to get about quite well. (Operation February, 1940).

a b c

Fig. 4. a, Roentgenogram taken on admission of W. W. (Case 3), male, aged 73 years. Operation was performed in the routine manner and postreduction plates, b and c, show position of the lag screw. (Operation February, 1940).

portion of the greater trochanter attached to the distal fragment as a point of purchase for the flange of the screw.

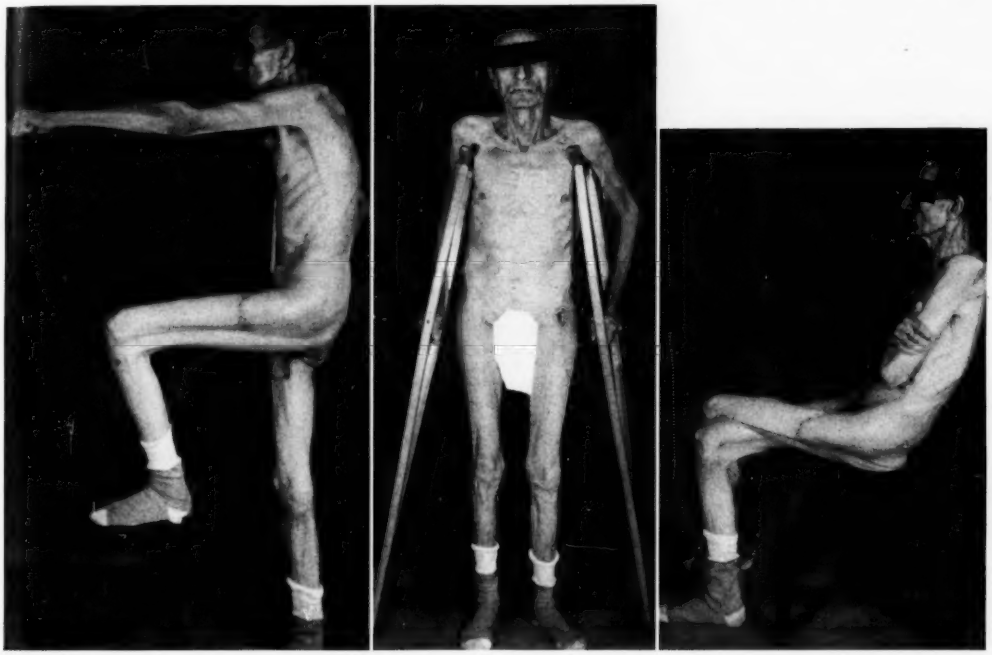
The advantages of this lag screw in fixation are chiefly those of early mobilization of the patient. This factor entails not only the reduction of the mortality rate and a great decrease in the period of hospitalization, but also added comfort and an improvement in the morale of the patient who is not cumbered with casts or traction apparatus of any sort.

Fig. 5. Case 3. Patient up in wheel chair on fourth day, showing type of dressing, the ACE bandage having been removed.

The instrument of fixation is made up of a unit of three separate parts: the lag screw, which is inserted well into the femoral head; a rectangular flange, which grasps the lateral surface of the greater trochanter and femoral shaft; and a nut, which when applied to the tail of the screw, over the flange, impacts and immobilizes the fractured fragments. The shaft of the screw, measuring 4 inches in length, terminates in a head made up of a wide wood-screw twist of six turns which penetrates and grasps the trabecular bone of the femoral head. The threaded tail of this instrument contains a slot which is adapted to receive the brace during its insertion and also to lock the flange to prevent its rotation after insertion. The rectangular flange, measuring five-eighths of an inch wide by two and a quarter inches long, is sufficiently large to afford a distribution of the lines of force over a wide surface of bone along the lateral portion of the greater trochanter and femoral shaft. In addition to this armamentarium a drill is needed to penetrate the cortex of the bone prior to insertion of the screw and a wrench for the turning of the nut.

THE TECHNIQUE OF OPERATION

One hundred milligrams of novocain is injected to produce spinal anesthesia, and an arthrotomy is performed after the method described by Cubbins and his co-workers. The skin incision extends from a point approximately 1 inch inferior to the anterior iliac spine, distally in a vertical plane about 8 inches, and then curves laterally a distance of some 5 inches. A cleavage plane is then sought lying between the tensor fascia lata on the lateral side and the sartorius on the medial side. The insertion of the former muscle into the iliotibial tract of the fascia lata is then divided at



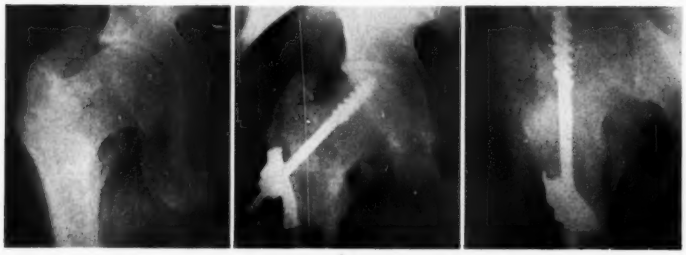
a b c

Fig. 6. Case 3. Crutches used 2 weeks after operation, without weight bearing. Three weeks after operation there is complete and painless motion of the involved hip, a, b, c. Crutches were discarded 8 weeks after operation and cane was used for 2 weeks. When last seen the patient was walking well and without a limp.

right angles so that the skin and the underlying muscle can be turned laterally as a flap. By the retraction of the rectus femoris and sartorius muscles medially the joint capsule is readily identified and a cruciate incision is made to expose the femoral neck and head. Very little bleeding is encountered if the branches of the lateral femoral circumflex vessels are identified and ligated as they pass through the operative field. The vastus lateralis muscle originating from the lateral surface and base of the greater trochanter is then split in a vertical plane, and a mastoid retractor is placed so as to expose the shaft of the femur in this region.

When the fracture site has been exposed and reduced by the Leadbetter maneuver, a drill hole is made from the lateral surface of the femoral shaft about 1 inch distal to the base of the greater trochanter, extending through the cortex and partially into the head of the femur. After the desired length is determined by direct measurement, the lag screw is inserted under visual surveillance, the exposed femoral head and neck being used as landmarks. The flange is then applied and the nut is tightened so as to reduce and hold the intertrochanteric fracture firmly. It is important that the flange be bent to fit the lateral contour of the bone without the interposition of soft tissues, for, should this be neglected, necrosis of the crushed soft tissues will result in the loosening of the screw.

The only deep structures which require suturing are the joint capsule and the insertion of the tensor fascia lata muscle. The remaining split muscle planes approximate themselves quite readily without fixation. Black silk is used throughout as a suture material. Before the closing of the wound, about 10 grams of sulfanilamide powder are sprinkled into the joint cavity and depths of the wound. An ACE bandage is applied over the sterile dressing as a hip spica in an effort to eliminate any possible dead space. The operative procedure consumes from 30 minutes to 1 hour depending upon the type of fracture, the ease of reduction, and the rapidity of fixation. Spinal anesthesia affords very good relaxation which is an important factor in approximation of the fragments. In our experience the operation has not seemed to cause shock and the patients in retro-



a b c

Fig. 7. a, Roentgenogram taken on admission of E. C. (Case 4), male, aged 53 years, showing considerable comminution of intertrochanteric region. Routine operation with insertion of lag screw was performed under direct vision. Results are shown in b and c. The patient was up in a wheel chair on the tenth day and was walking with the aid of crutches 2 weeks after operation. Three weeks later weight bearing was permitted and 12 weeks after operation he was walking without support. Motion was free except for abduction which was somewhat limited.

spect do not complain of discomfort resultant from this procedure.

The postoperative program followed is to have the patient propped up in bed 12 hours after the operation. The lower extremities are not encumbered by any traction apparatus and are left to roll freely about in bed. By the end of the second week, and in most cases within the first week, the patient is up in a wheel chair for short periods daily. Approximately 2 to 3 weeks after operation the patient is walking with the aid of crutches without weight bearing and after a period of 5 to 6 weeks weight bearing is permitted. The crutches are discarded in about 8 to 9 weeks and a cane is used if the patient so desires. Thus the patient with an intertrochanteric fracture is rehabilitated within a period of about 2 months.

EVALUATION

As in the case of the Smith-Petersen nail, insertion of the lag screw may be accomplished in one of two ways; either, through a small lateral incision over the base of the greater trochanter, in which case the progress of the screw is determined by repeated roentgenograms, or, by direct vision through exposure of the fracture site and the femoral neck and head. The lag screw was primarily devised for insertion by the former method, but for reasons to be discussed, these cases herein presented were reduced and immobilized by the latter technique.

Brittain, in discussing the disadvantages of the open operation and insertion of the Smith-Petersen nail under direct vision, raised the following objections: (1) Complete reduction by means of open operation is by no means certain; (2) the operation is a difficult one and undoubtedly carries a certain mortality; (3) radiology on the operating table, when there is a large incision, undoubtedly exposes the patient more to risks of infection than when the incision is confined to one-half inch; (4) there is frequently a certain amount of fibrosis associated with the opening of the capsule of the hip joint with resultant limitation of motion.

In the St. Louis City Hospital prior to August, 1939, the vast majority of the fractures of the femoral neck had been nailed by the closed method, but since that time most of the fixations have been accomplished by the open operation. This latter exposure afforded such an excellent view of the fracture site that it was adopted for the introduction of the lag screw as well. Though the points raised by Brittain refer specifically to fixation of fractures of the femoral neck by the Smith-Petersen nail, the same objections might well be raised to the open fixation of intertrochanteric fractures with the lag screw. Granted that the technique of open operation is somewhat more difficult, this factor should not be used as an excuse for its rejection, because actual visualization of the fracture site affords not only a better opportunity for exact reduction and fixation but also permits a testing of the solidarity of the immobilized fragments. This last is accomplished by motion of the thigh while observing the point of fracture. There is no need for radiological apparatus in the operating room, for the course of the screw can be determined by direct measurement of the exposed femoral head and neck. Thus there is need for only two sets of roentgenograms, one before operation to diagnose the type of fracture, and one after the operation to verify the success of fixation.

One of the hazards of orthopedic surgery has been infection and there are few fields of surgery

in which this complication can cause greater havoc. Jensen and his co-workers have presented a series of compound fractures in which the local implantation of sulfanilamide greatly reduced the percentage of wound infections. Stimulated by this report a policy was adopted of implanting about 10 grams of sulfanilamide powder in the operative wound, and this simple but effective measure has proved to be of definite value in the prevention of infection.

It may appear to some that arthrotomy is an unnecessary procedure because intertrochanteric fractures are extracapsular in position, yet, in order to direct the screw accurately and determine the depth of insertion, the femoral neck and head must be exposed. Experience both with the lag screw and Smith-Petersen nail has given no reasons to indicate that arthrotomy has resulted in a lack of free motion which might be ascribed to fibrosis of the joint capsule.

The limitations of this method of fixation are well recognized, for not every type of trochanteric fracture can be immobilized by the lag screw. In order to compete with extracapsular fractures the surgeon must be familiar with a varied armamentarium which should also include such factors as the Hodgen splint, varieties of the Whitman cast, and well leg traction. Each case may then be investigated from the standpoint of the type of fracture, age, economics, etc., and the final verdict thus determined. Since union of intertrochanteric fractures is the rule it is possible to determine the end-results at a much earlier date than is the case in femoral neck fractures, in which bone absorption and nonunion are encountered as complications. It is not necessary to remove the lag screw after union has occurred, though this is readily accomplished through a small incision over the tail of the screw. In certain cases the projecting tail of the screw is covered with a bone callus which tends to eliminate this as a possible source of irritation.

CONCLUSIONS

1. The mortality rate in intertrochanteric fractures of the femur is greater than that in fractures of the femoral neck.

2. Recent medical literature stresses the therapy of intracapsular fractures to the relative neglect of trochanteric fractures.

3. Four cases of intertrochanteric fractures of the femur are presented in which the lag screw was used as a method of internal fixation.

4. It is believed that in selected cases this procedure will result not only in a reduction of the mortality rate but also in a much shorter period of hospitalization.

5. It would appear that best fixation is obtained by open reduction and insertion of the lag screw under direct vision.

BIBLIOGRAPHY

1. Anderson, R. A. A new method for treating fractures utilizing the well leg for countertraction. Surg., Gynec. & Obst., 1932, 54: 207.
2. Brittain, H. A. Insertion of the Smith-Petersen nail into the femoral neck. Brit. M. J., 1936, 1: 838–840.
3. Cubbins, W. R., Callahan, J. J., and Scuderi, C. S. Fractures of the neck of the femur. Surg., Gynec. & Obst., 1939, 68: 87–94.
4. Henderson, M. S. Internal fixation of fractures of the neck of the femur. Arch. Surg., 1937, 35: 419–430.
5. Hodgen, J. T. On fractures, lecture 9. St. Louis M. & S. J., 1871, 8: 228.
6. Jensen, N. K., Johnsrud, L. W., and Nelson, M. C. The local implantation of sulfanilamide in compound fractures. Surgery, 1939, 6: 1–12.
7. Key, J. A. Internal fixation of trochanteric fractures of the femur. Surgery, 1939, 6: 13–23.
8. Leadbetter, G. W. Treatment for fracture of neck of femur. J. Bone & Joint Surg., 1933, 15: 931–940.
9. Leydig, S. M. Fractures of the neck of the femur treated with the Smith-Petersen nail. Surg., Gynec. & Obst., 1939, 68: 713–717.
10. Leydig, S. M., and Brookes, T. P. Treatment of pertrochanteric fracture of the femur with a lag bolt. J. Missouri State M. Ass., 1940, 37: 354–357.
11. Moore, A. T. Fracture of the hip joint. Surg., Gynec. & Obst., 1937, 64: 420–436.
12. Rowlette, A. P., Haslem, J. R., Siegert, R. B., Morris, H. D., and Key, J. A. Results obtained by subcutaneous pinning of fractures through the neck of the femur. J. Am. M. Ass., 1936, 107: 1610–1614.
13. Smith-Petersen, M. N., Cave, E. F., and Vangorder, G. W. Intra-capsular fractures of the neck of the femur; treatment by internal fixation. Arch. Surg., 1931, 23: 715–759.
14. Weiner, David. Personal communication to the author. Data to be published.

COMBINED TRACTION-COMPRESSION METHOD FOR THE TREATMENT OF BICONDYLAR FRACTURES OF THE TIBIA

ROBERT A. WISE, M.D., F.A.C.S., New York, New York

COMBINED traction and compression are required for the satisfactory reduction of bicondylar fractures of the tibia. These injuries are produced by a force which drives the hard cortical shaft of the tibia into the soft expanded cancellous portion of the tibial plateau, resulting in a splitting, separation, and depression of the condyles. It is clear that any satisfactory method of treatment must correct the upward thrust of the tibial shaft as well as reduce the lateral displacement and depression of the tibial condyles. Traction alone without compression of the condyles is insufficient; compression without traction will result in unsatisfactory alignment of the fragments. A combination of both traction and compression is necessary. Moreover, these forces must be applied in such a manner that they can be maintained until the fracture is firmly united. To apply compression by means of a carpenters' clamp and then, of necessity, to release it will frequently result in a recurrence of the deformity. To maintain traction by means of a casing is impossible.

It is the purpose of this paper to present a simple method of applying continuous traction and compression for the reduction and fixation of displaced bicondylar fractures of the tibia. The traction is obtained by means of a Kirschner wire which is inserted through the calcaneus; the compression, by a sleeved-wire (1) inserted through the tibial condyles.

The following case report demonstrates the application of this method.

CASE REPORT

J. J., a male, aged 27 years, was admitted to Knickerbocker Hospital on June 6, 1939. He stated that while riding a bicycle the front wheel suddenly caught in its frame and he was thrown forward striking his right leg against the curbing.

Examination revealed a swollen, tender, discolored right knee. There was evident widening of the tibial plateau and the lateral condyle and head of the fibula were abnormally prominent. There was moderate valgus deformity and slight external rotation of the leg. The knee joint was unstable with a wide range of anteroposterior and lateral mobility.

Roentgenogram (Fig. 1) showed a comminuted bicondylar fracture of the tibia with marked outward displacement of the lateral and depression of the medial condyle.

From the Fracture Service of Knickerbocker Hospital.

Read before the Surgical Section of the New York Academy of Medicine, October 4, 1940.

Russell traction was applied to the right leg for 6 days with resulting improvement in the alinement of the fragments but with no change in the outward displacement of the lateral condyle or the depression of the medial condyle. It was evident that compression of the condyles, as well as traction in the long axis of the leg, was necessary.

Combined continuous compression and traction was applied on June 13, 7 days following the injury. The compression sleeve used consists of three parts: (1) a Kirschner wire of medium diameter to which is welded a fixed metal bead and washer; (2) a metal sleeve which slips over the wire; and (3) a threaded collar with set screw and nut.[1]

Technique. Under nitrous-oxide-oxygen anesthesia, a Kirschner wire was inserted through the calcaneus and traction was applied to the leg. An incision 1 centimeter in length was made over the lateral tibial condyle midway between its anteroposterior diameter and 1.5 centimeters below its articular surface. The sleeved-wire with the fixed bead and washer was then inserted through the upper end of the tibia, emerging on the inner side of the knee through the medial condyle, the washer placed against the periosteum of the lateral condyle. A 1 centimeter incision was made at the point of exit and the metal sleeve slipped over the wire and brought into contact with the medial condyle. The threaded collar was then placed on the wire and fixed by means of its set screw. The nut was turned, and as it approached the medial condyle, compression was exerted through the sleeve forcing the condyles together.

Roentgenogram (Fig. 2) showed marked improvement in the position of the fragments. The leg was placed on a Boehler frame with 12 pounds of traction applied through the calcaneus and with compression maintained by means of the sleeve (Fig. 3).

After-care. Baking and massage with quadriceps exercises were begun early. The compression force was unchanged but the traction was reduced to 5 pounds after 5 weeks. Seven weeks after reduction, under local anesthesia, the compression wire was removed from the upper end of the tibia and the Kirschner wire was withdrawn from the calcaneus. A plaster casing was applied from the toes to the midthigh, with the knee in 15 degrees of flexion. The patient was allowed up on crutches and discharged 4 days later. The casing was bivalved 9 weeks after reduction and removed daily for massage and active knee motion. The incisions at the upper end of the tibia had healed per primam. Three months after reduction, a walking caliper brace was applied. Unsupported weight bearing was allowed 6 months after the injury. Examination of the patient in May, 1940, 11 months after reduction, revealed a stable, painless knee with complete extension and 135 degrees of flexion (Figs. 4 and 5). There was no anteroposterior motion of the knee joint and only slight lateral mobility. Roentgenogram (Fig. 6) showed firm healing of the fracture.

The method described makes possible the continuous action of the two forces required. Continuous compression could be obtained by a bolt but

[1]Made by Depuy Mfg. Co.

Fig. 1.

Fig. 1. Before reduction. Note marked outward displacement of lateral condyle and depression of medial condyle.

Fig. 2.

Fig. 2. After reduction.

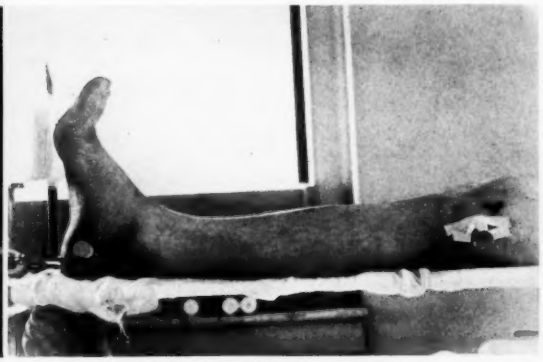


Fig. 3.

Fig. 3. Showing compression sleeve in tibial condyles and Kirschner wire through calcaneus.

Fig. 4.

Fig. 5.

Fig. 6.

Fig. 4. Appearance of leg 11 months after reduction.
Fig. 5. Degree of flexion present 11 months after reduction.
Fig. 6. Roentgenogram 11 months after reduction.

the sleeved-wire has the advantage of simplicity of insertion and removal with minimal trauma to the cancellous bone.

The points chosen for the insertion and exit of the compression wire will vary with different displacements and should be determined after careful study of the roentgenograms. In some cases the wire will be introduced 1 centimeter below the articular surface, in others a position several centimeters lower will effect the best compression. As the normal landmarks about the knee are often obliterated by soft part swelling, it is advisable to place a marker across the upper end of the tibia in what is considered the desired position and to take an anteroposterior roentgenogram. The correct position in the longitudinal plane for the insertion of the wire can be easily determined from the position of the marker. In the vertical plane, the wire should be introduced into the center of the tibia, a point easily selected by means of palpation.

Arthrotomy is indicated in many badly displaced bicondylar fractures because of severe injury to the semilunar cartilages and lateral ligaments. Because the methods for reduction and fixation of the bony fragments at open operation have not always been successful, it is suggested that if arthrotomy is performed, the displaced

condyles may be reduced and fixed by the combined traction-compression method where is here described.

SUMMARY

1. A method combining continuous traction and compression is reported.

2. The value of the combined traction-compression principle in the reduction and fixation of a bicondylar fracture of the tibia is demonstrated.

3. Traction is obtained through a Kirschner wire in the calcaneus.

4. Compression is applied by means of a compression sleeve which is inserted through the condyles.

REFERENCE

1. Wheeldon, T. A sleeved-wire method of fixation of fractures. J. Bone & Joint Surg., 1939, 21: 210–214.

RELATION OF PYELONEPHRITIS TO TOXEMIAS OF PREGNANCY

GEORGE C. PRATHER, M.D., F.A.C.S., and WESTON SEWALL, M.D.,
Boston, Massachusetts

DURING recent years Peters (8–11) has been foremost in presenting data which might suggest pyelonephritis as a possible cause of toxemia of pregnancy, the general term describing certain complications which occur during gestation, whose symptoms at times include headache, visual disturbances, irritability, nausea, vomiting, epigastric pain, rapid gain of weight, and, perhaps, convulsions. Frequent clinical findings are edema, hypertension, and albuminuria. It is evident that many of the signs and symptoms of toxemia are also common in various types of renal disease. So many theories of the cause of toxemia have been advocated that it is evident that no one yet knows the answer to this problem.

General agreement has existed during the past few years that vascular change (4) is the basic pathological conception. Pathological changes in toxemia, as in essential hypertension, are found more commonly in the kidneys than in other organs of the body (3). While the changes accompanying these troubles in the kidney are somewhat variable in both their extent and their variety, Fahr, Bell, Baird and Dunn have reported thickening of the capillary walls of the glomeruli due particularly to thickening of the basement membrane in the capillary tufts. The increase in bulk produced by the thickened connective tissue membrane contributed to the obstructive effect in the capillary.

Although it is not certain what initiates this clinical or pathological condition in pregnant women without previous vasculorenal disease, the symptoms which the toxemias and certain renal diseases possess in common have led to a broader conception of the problem. The more comprehensive point of view can be visualized if one compares the classification of toxemias today with that of 20 years ago (14). At that time nephritic toxemia, pre-eclamptic toxemia, and eclampsia formed the only subdivisions of this subject. Contrast today's proposed classification (Table I) recently offered by Kellogg and Reid, which is cognizant of the fact that renal conditions existing during pregnancy may simulate pre-eclampsia and eclampsia.

Pyelonephritis as the initial lesion of a trend resulting in progressive deterioration of the kidney has been emphasized by Weiss and Parker, by Longcope, and by others interested in the relation of chronic pyelonephritis to hypertension. Since the albuminuria and hypertension of toxemia of pregnancy may be associated with renal disease, it seems reasonable to investigate the incidence of toxemia following pyelonephritis in pregnancy. Mussey and Lovelady recently stated that pyelitis of pregnancy is not prone to cause pre-eclamptic toxemia or eclampsia. Although we may not agree with all of the conceptions and

TABLE I.—CLASSIFICATION OF TOXEMIAS OF PREGNANCY—KELLOGG AND REID—1939

Group A

I. Hypertensive or arterial vascular disease
   a. Benign
      Mild
      Severe—cardiorenal
   b. Malignant
II. Renal disease
   a. Glomerulophritis
      Acute
      Chronic
        Mild
        Severe
   b. Pyelonephritis
      Acute
      Chronic
   c. Other forms of severe renal disease. Nephrosis, polycystic kidneys, and other congenital anomalies of the kidneys

Group B

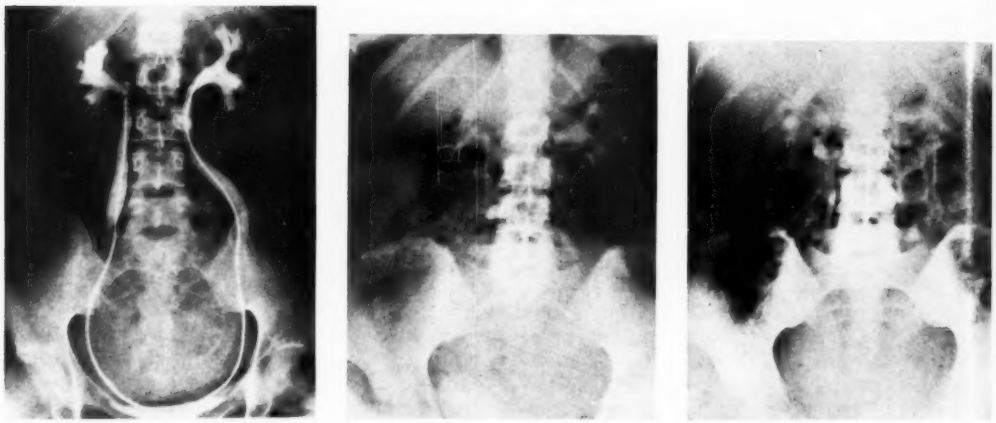
I. Mild pre-eclampsia
II. Severe pre-eclampsia (Preconvulsive)
III. Eclampsia

Group C

I. Unclassified (unknowns)
   a. Those patients in whom a definite diagnosis cannot be made to allow them to fall into Group A or B (i.e., glomerulonephritis suspects)
   b. Many will fall into the above known groups postpartum, but insufficient data before or in the early months of pregnancy, make it imperative to exclude them from statistical data except if autopsy findings ultimately allow them to be put in either Group A or B

From the urological and obstetrical departments of the Boston Lying-in Hospital.

Read June 20, 1940 before the American Association of Genito-urinary Surgeons.



a b c

Fig. 1. a, Primipara with left pyelonephritis, in 1931. b, Same patient in early pregnancy in 1939. The urine showed no infection. c, Same patient immediately postpartum in 1939. Late pregnancy changes not yet resolved.

conclusions presented by Peters, we acknowledge the importance of his success in focusing attention to the possible association of pyelonephritis to the toxemias of pregnancy. Of 320 cases with a diagnosis of toxemia studied by Peters, 41, or 13 per cent, had had pyelitis or pyelonephritis. The opinion was verified by autopsy in 11 of the 41 cases. Of 25 toxemia patients who came to autopsy during a 14 year period, Peters reported that in 11, or 44 per cent, pyelonephritis was found. However, closer scrutiny of the autopsy data which were presented would lead us to believe that only 4 of the 11 cases, approximately 10 per cent, showed chronic pyelonephritic changes.

The important data supplied by Peters have been rather startling because of the relatively high incidence of pyelonephritis which he found in toxemia. We, therefore, recently decided to review a series of patients at the Boston Lying-in Hospital who we feel had pyelonephritis associated with at least one pregnancy, and who

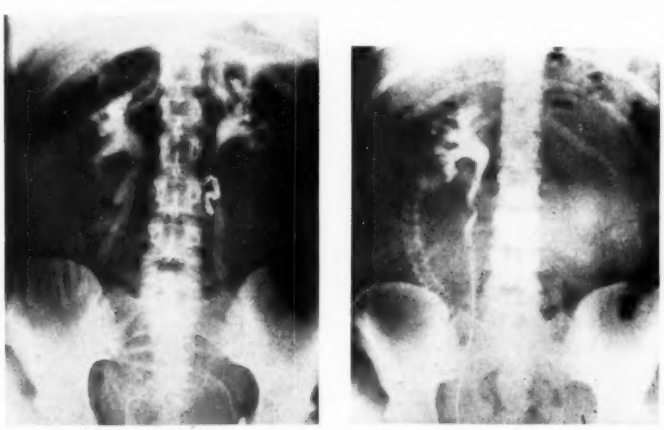
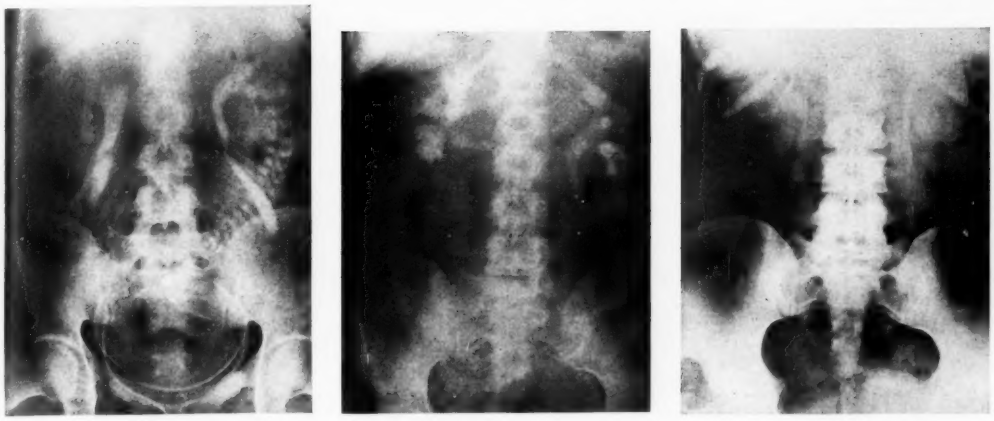


Fig. 2. a, left. Patient with pyelonephritis in sixth month of pregnancy. Moderate pregnancy changes in right ureter and kidney. b, Same patient 1 year later during another pregnancy. Urine was uninfected. There is less anatomical change than during the previous pregnancy.



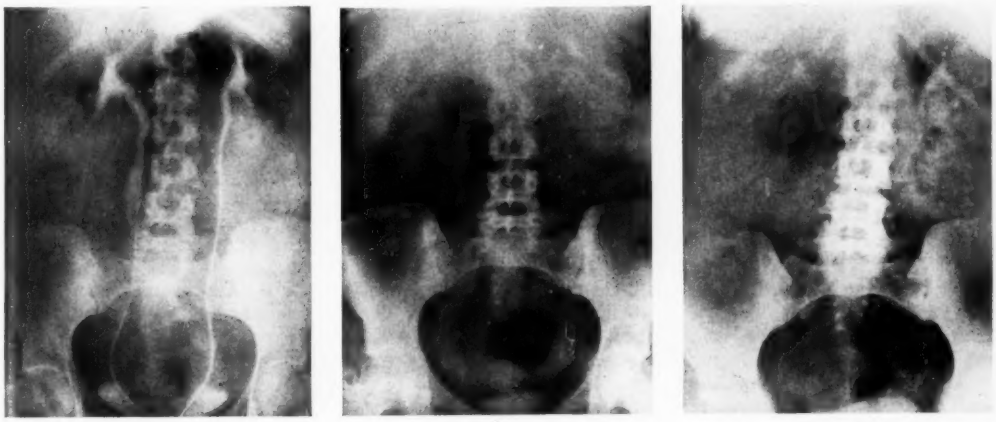
a b c

Fig. 3. a, A quadripara with pyelonephritis on the right side in 1930 during the eighth month of a pregnancy. b, The same patient with pre-eclampsia during a pregnancy in 1933. c, The same patient postpartum. There is evidence that a good anatomical recovery was made from the changes of pregnancy.

returned during a later year in a pregnant state. Such a review may give data as to how frequently toxemia follows the pyelonephritis associated with pregnancy.

The data for this paper are based on the observations and records of 72 patients with pyelonephritis and pregnancy during the years 1930 to 1939. Only patients who had one or more pregnancies subsequent to the pregnancy with pyelonephritis were used. Of the 72 patients, 42, or 58.3 per cent, were primipara; 30, or 41.7 per cent, were multipara. Seventy had pyelonephritis during pregnancy; 2 had acute pyelonephritis immediately postpartum while in hospital. Forty-three, or approximately 60 per cent, were in a febrile phase while in hospital, leaving 29, or 40 per cent, in an afebrile, subacute stage at the time of observation.

Further incidental clinical data of the patients forming our group indicated that pyelonephritis affected the right kidney in 48.5 per cent of the cases, the left kidney in 19.7 per cent of the cases, and in 31.8 per cent the inflammatory process was bilateral.



a b c

Fig. 4. a, Tripara with bilateral pyelonephritis in 1930. b, Same patient with toxic separation of placenta during a later pregnancy. c, Same patient at a later period, non-pregnant.

a b c

Fig. 5. a, Tripara, in 1931, with pyelonephritis in the ninth month of pregnancy. The bony pelvis is abnormal. b, Same patient in 1936, during her fifth pregnancy. Although there is bilateral hydronephrosis and hydroureter, the urine remained sterile. c, Same patient postpartum after her fifth pregnancy. It is evident that there has been a good anatomical recovery of the kidneys and the ureters.

The records of these patients suggested a past history of pyelonephritis in 16.6 per cent, half of whom had had the disease with a previous pregnancy, the remaining half having had pyelonephritis before the onset of any pregnancy.

Our diagnoses were made by cystoscopic studies in 34 patients, clinical and laboratory findings in 38. Laboratory data revealed a bacillary type of urinary infection in 91.3 per cent, gram positive cocci in 5.1 per cent, bacilli and cocci in 3.6 per cent.

Renal function tests were not done as routine during the hospital admission for pyelonephritis, so that we do not have sufficient data from urea clearance studies and concentration tests to draw any conclusions. The nonprotein nitrogen in 40 cases was reported as 21 to 33 milligrams per 100 cubic centimeters of blood, and the blood uric acid in 38 cases was recorded as 2.3 to 4.1 milligrams per 100 cubic centimeters of blood. Although we realize that blood chemistry does not detect slight diminution of renal function, it is evident that renal decompensation did not exist.

X-ray data were obtained in 55 patients—26 having had intravenous pyelography, the remaining 29 retrograde study. The dilatation of the ureters and pelves (Fig. 1) and the ureteral kinks were not extraordinary to anyone familiar with urological changes during pregnancy. The renal and ureteral dilatation in the subsequent pregnancy (Fig. 2) never exceeded that found with the first pyelonephritis, irrespective of whether the subsequent pregnancy was normal or complicated by recurrent pyelonephritis or toxemia. In general, patients with toxemia appear to have less ureteral and pelvic distortion (Figs. 3 and 4) by intravenous pyelography than the normals. Extreme degrees of distortion and dilatation were observed frequently in patients with normal urine sediments and without clinical signs (Fig. 5) of pyelonephritis. The anatomical recovery following the physiological dilatation of pregnancy is impressive but is subject to continued distortion if abnormalities were present before pregnancy, or if inflammatory changes in the pelvis or ureter go on to fibrosis.

Our primary interest in this study was not the findings in pyelonephritis, but rather how many later pregnancies were normal and how many were complicated by toxemia.

Of the 72 patients with pyelonephritis, 47, or 65.28 per cent, had normal pregnancies at a later date. As a matter of fact, 15 of the 47 had further multiple normal pregnancies—a total of 67 normal pregnancies in 47 patients. The time interval between the pyelonephritis during pregnancy and the normal pregnancy varied between 1 and 9 years, an average interval of 3.62 years. Frequent blood pressure recordings were normal during the subsequent pregnancies in all 47 patients. Blood pressures during the normal later pregnancies were about the same as during pyelonephritic pregnancy in 34 patients; in 13 the readings averaged lower during normal pregnancy. Six of 47 patients had the slightest trace of albumin in a voided specimen just prior to term.

One normal pregnancy following a pyelonephritic pregnancy does not guarantee freedom from complications during a still later pregnancy. This fact is illustrated in 6 patients who developed pyelonephritis after having a normal intervening pregnancy, and 1 patient who developed toxemia of pregnancy after a normal intervening pregnancy.

Interest, of course, will be centered on those who had pyelonephritis during one or more pregnancies, and who in a later pregnancy developed toxemia. In our series of 72 patients who had pyelonephritis associated with pregnancy, and who later returned to hospital in a pregnant state, 9, or 12.5 per cent, developed toxemia. The hospital diagnosis as to the type of toxemia was pre-eclampsia in 8, eclampsia in 1, (toxemic separation of the placenta with albuminuria in 1). The time interval between pyelonephritis in pregnancy and the toxemic pregnancy ranged between 1 and 9 years. The average interval was 3.45 years, essentially the same interval as mentioned above in discussion of the group who had subsequent normal pregnancies following pyelonephritis. Apparently the time interval is not important. Our data as to whether the urinary infection had cleared during the interval are incomplete. We are certain that of the 9 who developed toxemia, 2 patients had urines free of infection during the interval between pregnancies and 2 were known to remain infected. At the time of the pyelonephritis 4 were primiparas, 5 were multiparas. At the time of toxemia 3 were secundipara, 1 was a tripara, 1 was a quadripara, 3 were quintipara, and 1 was a decipara. The toxemia occurred in the first pregnancy following pyelonephritis of pregnancy in 7 of the 9. In 2 there was an intervening pregnancy with no indication of toxemia.

Renal function tests during the pregnancy with toxemia were not done as routine except for the nonprotein nitrogen, which was normal as one might expect. Table II shows the blood pressure readings in 9 patients with pyelonephritis who later developed toxemia. The toxemia was sufficiently severe in 5 of the 9 patients to warrant interruption of the pregnancy.

Because of the current interest in the relation between blood pressure and pyelonephritis, we present a meager amount of data which may be of interest. Of the 72 patients in our series there were 8, or 11.11 per cent, who during the pregnancy with pyelonephritis had, on one or more occasions, a blood pressure recorded of 140/90 or over. Four were in the ninth month of pregnancy, 2 were in the seventh month, 2 were in the sixth month. Three of the 8 had a past history of renal disease. The 8 patients just mentioned had 10 pregnancies following the one in which pyelonephritis and hypertension were observed. The time interval was 1 to 6 years, an average of 3.2 years. In the 10 pregnancies which followed, recurrent pyelonephritis developed in 5, but blood pressures remained below 130/85 at all examinations. Three normal pregnancies followed with all blood pressure readings 128/80 or below. Two developed toxemia with hypertension. In a follow-up of the 8 patients mentioned after an average interval of 3.7 years from the time of pyelonephritis with hypertension, all had blood pressure readings below 135/84. Only 1 patient had the slightest possible trace of albumin. Thus, in a small group of 8 patients with pyelonephritis and hypertension, toxemia developed at a later pregnancy in 25 per cent, which is double the incidence following pyelonephritis in general during pregnancy. However, our limited data fail to suggest any permanent elevation of blood pressure following pyelonephritis during a 3 year follow-up period.

TABLE II.—BLOOD PRESSURE AND ALBUMIN

Case Number	Pyelonephritis			Toxemia		
	Year	Blood Pressure	Albumin	Year	Blood Pressure	Albumin
2	1935	118/74		1939	134/78	S.P.T; S.T.
27	1937	110/86		1939	132/94	S.P.T.
30	1936	150/110	V.S.T.	1939	150/84	L.T.
42	1930	108/80		1933	144/110	
47	1930	94/58		1931	170/114	L.T.
49	1930	108/80		1933	146/98	V.S.T.
64	1930	140/		1931	80/68	T.
65	1930	102/62		1933	(Hemorrhage) 105/65	S.P.T.
71	1930	114/60		1939	170/100	

On the basis of maternity hospital admissions, pyelonephritis has an incidence of 1 to 2 per cent (12). By the same standards, toxemia of pregnancy has an incidence of about 10 per cent (15). We have found that toxemia of pregnancy follows pyelonephritis associated with pregnancy in 12.5 per cent.

Not feeling competent to make accurate deductions from these simple figures we called upon Mr. Philip Rulon, who teaches statistics at Harvard University, for advice. His informal opinion was as follows:

A. The incidence of pyelonephritis in pregnancy is 1 to 2 per cent.

B. The incidence of toxemia in pregnancy is 10 per cent.

The incidence of toxemia of pregnancy following pyelonephritis associated with previous pregnancy is 12.5 per cent.

Pyelonephritis is not a cause of toxemia of pregnancy.

The data for the proper deductions as to possible cause and effect should be tabulated in the manner here used; namely, to see how frequently disease B—toxemia—follows disease—A, rather than the way in which Peters studied the problem; namely, how often disease A—pyelonephritis—occurs in disease B—toxemia. (According to Mr. Rulon there are too many variables in Peters's method of approach to warrant conclusions.) As for our data, which indicate an incidence of pyelonephritis in pregnancy of 1 to 2 per cent, an incidence of toxemia of approximately 10 per cent, and toxemia following pyelonephritis in pregnancy in 12.5 per cent, Mr. Rulon states that if the same ratio held in 500 cases (we have only 72) we should be well justified in stating that pyelonephritis is not a cause of toxemia of pregnancy.

BIBLIOGRAPHY

1. Baird, D., and Dunn, J. S. J. Path. & Bacteriol., 1933, 37: 291.
2. Bell, E. T. Am. J. Path., 1932, 8: 1.
3. Fishberg, A. M. Hypertension and Nephritis. 4th ed. Philadelphia: Lea & Febiger, 1939.
4. Irving, F. C. Canadian M. Ass. J., 1939, 40: 137.
5. Kellogg, F. S., and Reid, D. F. To be published.
6. Longcope, W. T. Chronic bilateral pyelonephritis. Ann. Int. Med., 1937, 11: 149.
7. Mussey, R. D., and Lovelady, S. B. Am. J. Obst. & Gynec., 1940, 39: 236.
8. Peters, J. Yale J. Biol. & Med., 1937, 9: 311.
9. Idem. J. Am. M. Ass., 1938, 110: 329.
10. Peters, J., et al. Am. J. Obst. & Gynec., 1936, 32: 911.
11. Peters, J., and Zimmerman, H. Tr. Ass. Am. Physicians, 1936, 51: 287.
12. Prather, G. C. Urological complications during pregnancy. J. Indiana State M. Ass., 1937, 30: 371–379.
13. Weiss, S., and Parker, F., Jr. Pyelonephritis. Medicine, 1939, 18: No. 3.
14. Williams, J. Whitridge. Obstetrics. 4th ed. New York and London: D. Appleton & Co., 1921.
15. Ibid. 7th ed., 1936.

MIXED INTRACRANIAL GLIOMAS

The Diagnostic and Prognostic Significance of Adequate Histological Examination

DONALD MUNRO, M.D., F.A.C.S., JESSE E. EDWARDS, M.D., and WILLIAM O. RUSSELL, M.D.,
Boston, Massachusetts

IT IS axiomatic that the accuracy of the diagnosis and prognosis of any neoplastic growth will vary directly with the amount and accuracy of the information available in regard to its histology and its location in the body. Such generalities are particularly applicable to the intracranial neoplasms. There are, to be sure, characteristics peculiar to this particular group of tumors which cause them to differ in detail although not in principle with these statements. For example, the usual intracranial neoplasm does not metastasize by way of the blood or lymph channels, but rather spreads locally either by expansion or by radial invasion. Such tumors, if irremovable, cause death, however, by virtue of the profound alterations produced in general, rather than local, central nervous system physiology. Thus, regardless of its histological character, any type of intracranial tumor can and will prove fatal when inaccessible and if properly placed in relation to the nervous structures around it. One phase of the brain tumor problem and of any attempt to estimate its end-results has to do, therefore, with a demonstration of the exact position of the tumor. This is well recognized and all of the modern advances in the therapy of intracranial tumors have depended, at the last analysis, upon the ability of the surgeon to make previously inaccessible areas accessible.

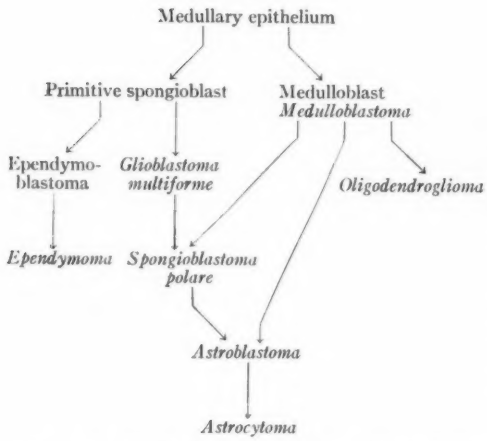
It is less well appreciated, however, that the histological make-up of the tumor is as important from a diagnostic and therefore prognostic viewpoint as its exact location. A circumscribed cerebellar medulloblastoma may be more accessible than the mural nodule in the upper wall of a large astrocytomatous cyst of the same region. Yet, apparently adequate removal of both will produce a lifetime cure in the latter and a life expectancy of not more than a year in the former. Such a difference in prognosis is demonstrable histologically at the time of operation. The importance of this operative histological study has been minimized by some neurosurgeons just as the accuracy of so called pre-operative localizing signs has been overemphasized by some neurologists. At the last analysis, the final criteria of diagnosis and therefore removability must wait on exposure and adequate biopsy of the tumor either at operation or at autopsy.

From the Mallory Institute of Pathology and the Neurosurgcal Service of the Boston City Hospital, Boston, Massachusetts.

These requirements apply in particular to the gliomas. A long step toward effective understanding of these tumors was taken with the publication of Bailey and Cushing's classification (Table I). Bailey further points out in a later publication that "*each type of glioma is a distinct entity with its own idiosyncrasies* which it is important to recognize. Any attempt to describe 'glioma' as an entity only leads to confusion . . . *In general the gliomas composed of cells resembling those of the early stages of histiogenesis tend to develop more rapidly.*" Of the groups that are commonly recognized the *medulloblastoma* and the *glioblastoma multiforme* are tumors that are closest to, and the *astrocytoma* the one that is furthest from the original medullary epithelium. In between these extremes lie, in approximate order of histological youth, the oligodendrogliomas, pinealomas, ependymomas, polar spongioblastomas, and astroblastomas.

It is obvious that tumors of adjacent cellular age may appear as histological mixtures. There have been expressions in the literature which bear on this point. Penfield has emphasized that the cells of any given glioma are originally derived from one primitive cell. With increasing age, differentiation becomes gradually more and more complete. Theoretically, therefore, it is possible to find cells representing varying phases of this differentiation in any one tumor. He reports that this idea is consistent with actual experience so that, for example, a tumor growing largely as an astrocytoma may contain spongioblasts and astroblasts. Globus (3) and Levine have each observed gliomas in which there was a mixture of cell types throughout the tumor. They are of the opinion that these cell types represent phases of glial development, and they have termed these tumors transitional cell gliomas. Carmichael has indicated

TABLE I.



The relationships of the common cranial gliomas. (Modified from Bailey and Cushing's classification. The choroidal, pineal and neuroblastic groups are omitted for purposes of simplification.)

that one cannot place every glioma into some one of Bailey and Cushing's groups because it is common to find a mixture of cell types within these tumors. Furthermore, because gliomas frequently grow in part as polar spongioblastoma and in other areas as spongioblastoma (glioblastoma) multiforme, he has suggested the name "spongioblastic glioma" to include all tumors of the two types named. In tumors with greater cellular age, Carmichael has found some areas in which the tumor was growing as astroblastoma and others in which there was the appearance of astrocytoma. He suggested the name of "astrocytic glioma" to include all tumors of the astrocytic and astroblastic type whether occurring singly or together. Although those cases of Carmichael that showed a mixture of types were usually confined to either the spongioblastic or astrocytic groups, there were instances in which the tumor included elements from both. Others have also demonstrated a mixture of several types of glioma in isolated instances, among them being Globus and Strauss (4).

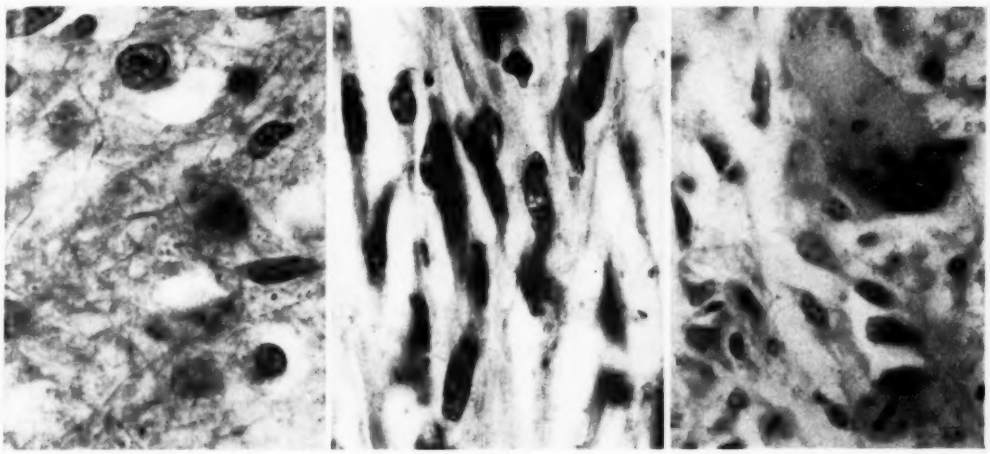
Gliomatous tumors composed of cells that are not developmentally adjacent should not be expected to occur under ordinary circumstances. Their frequent demonstration makes one suspect the orderly classification that thus places such cells at widely separated growth levels, and emphasizes what has already been recognized clinically, that is, that tumors that were histologically benign have had life cycles that were clinically malignant. Such a histological combination will, if recognized, materially influence the treatment accorded any given glioma. The recent demonstration of 9 such mixed gliomas is, on that account, worthy of attention. They occurred in the course of 4 years during which 142 verified intracranial tumors were seen on the neurosurgical service at the Boston City Hospital. Seventy-nine, 55 per cent, were gliomas and 28, 20 per cent, were meningiomas. All the other types formed a group of 35, 24 per cent. The presence in the entire group of 6 per cent of mixed gliomas has a diagnostic and prognostic significance that cannot be overlooked. This is especially true when it is realized that these same 9 cases constituted 11 per cent of all the gliomas we encountered.

Four of the mixed tumors showed 3, and the 5 others 2, cell elements. A part of every tumor was glioblastomatous, that is, the predominant cell was multiform, often a giant cell, had frequent mitotic figures, and gave every evidence of being an immature, actively growing tumor cell.

The balance of one of the tumors was classed as spongioblastoma polare, but this was the only one in which adjacent cell groups were co-existing alone.

Case 1 (N. S. 3244 and A-39-374). Male, aged 41 years. For one year previous to entrance, this patient had been having frontal headaches. For 3 months previous to entrance, he had had daily episodes of numbness in the right hand and forearm without paralysis. On the day of entry he had 2 right sided convulsive attacks, the last with loss of consciousness and with some involvement of the left side as well. On admission, he was irritable, unco-operative and disoriented. His general physical examination was negative. His blood pressure was 145/90 millimeters mercury. He had weakness of his right arm with astereognosis and loss of position sense of the fingers of his right hand. He was right handed and there was some indefinite aphasia. A lumbar puncture revealed an intracranial pressure of 130 millimeters water. The cerebrospinal fluid was clear with one white blood cell, a total protein of 27 milligrams per cent and a negative Wassermann and gold sol. A ventriculogram showed a marked displacement of the entire ventricular system to the right and downward. The ventricular fluids contained 7 and 27 milligrams per cent of total protein on the right and left, respectively. A left midparietal craniotomy was done and a large infiltrating cortical and subcortical tumor was found. This was biopsied and diagnosed as a glioblastoma multiforme. The dura was closed tightly, and the bone flap was replaced. The patient died 9 days after operation.

At autopsy, the brain weighed 1,500 grams. An area of operative interference 1 centimeter in diameter was present in the region of the left superior parietal gyrus. In the left parietal region serial sections showed a well circumscribed area 3 centimeters in diameter that was mostly in the white matter, but which infiltrated the gray matter slightly as well. This mass was yellow gray with firm periphery and softer central portions.



a b c

Fig. 1. a, Astrocytoma showing numerous neuroglial fibrils. Mallory's phosphotungstic acid hematoxylin stain. ×745. b, Fusiform cells arranged in parallel rows. No intercellular fibrils. This area is typical of a polar spongioblastoma. Mallory's phosphotungstic acid hematoxylin stain. ×745. c, Glioblastoma multiforme showing two mitoses and a tumor giant cell. Mallory's phosphotungstic acid hematoxylin stain. ×225.

Microscopically this tumor showed two fundamental pictures. The major part was growing as a polar spongioblastoma. There were spindle cells with long, fairly well stained cytoplasmic processes, an occasional mitosis, and no intercellular fibrils. This picture was similar to that seen in Figure 1b of Case 2. In a smaller number of fields the tumor failed to show any regularity and tumor giant cells similar to that in Figure 2c of Case 4 were found. We consider these latter areas characteristic of glioblastoma multiforme.

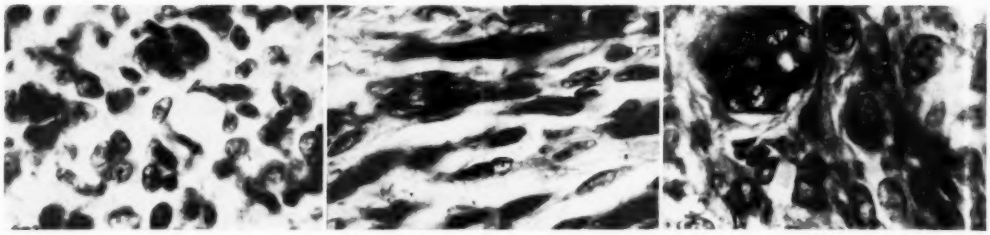
Four other tumors that contained both glioblastomatous and spongioblastomatous tissue had in one case an additional undifferentiated part that resembled medulloblastomatous tissue and in the 3 other cases additional astrocytomatous (twice) and oligodendrogliomatous sections as well.

Case 2 (Nerve, A-36-450). Female, aged 56 years. For 1 month previous to entrance she had complained of increasing weakness and staggering gait, falling to the left, transient diplopia, headache and drowsiness with difficulty in thinking. For a few days before admission, she had been vomiting and had felt weak. She lost 10 to 12 pounds in this month. There had been no injuries or illnesses in the past. General physical examination was negative except for pallor and signs of recent weight loss. She was drowsy and unco-operative. She showed a left hemiparesis including the lower facial region. The deep reflexes were increased on the left. There were bilateral Babinski, Oppenheim, and Gordon signs. There were high choked discs and she was unable to count fingers with the left eye at 3 feet. Her blood pressure was 90/60 millimeters mercury. She had a slight anemia and a positive blood Hinton. Lumbar puncture showed an intracranial pressure of 470 millimeters water with normal dynamics. The cerebrospinal fluid had 51 white blood cells, 10 per cent of which were polymorphonuclears, a total protein of 78 milligrams per cent, and a doubtfully positive Kahn test. Other specimens showed cells as high as 1,300, from 25 to 100 per cent polymorphonuclears and total proteins from 130 to 750 milligrams per cent. She died suddenly and untreated 8 days after admission.

At autopsy the brain weighed 1,270 grams. There was a moderate cerebellar pressure cone with widening and flattening of the cerebral convolutions. In the right cerebral hemisphere, there was a huge tumor mass extending posteriorly from the anterior tip of the right frontal lobe to a level 5 centimeters anterior to the tip of the occipital lobe. Laterally the tumor extended to the surface of the cerebral substance and medially to the lateral border of the right thalamus. The tumor tissue was soft yellowish white and possessed a purplish brown border.

Microscopically some areas of the tumor showed well differentiated cells with prominent intercellular fibrils staining purple with the phosphotungstic acidhematoxylin stain. These areas may be considered characteristic of astrocytoma (Fig. 1a). Other areas showed definite spindle-shaped cells whose cytoplasm stained fairly well. There were no intercellular fibrils. In these areas the tumor resembled a polar spongioblastoma (Fig. 1b). In other regions were poorly differentiated cells with mitotic figures and tumor giant cells characteristic of glioblastoma multiforme (Fig. 1c).

Case 3 (N. S. 3350, S-39-2709). Male, aged 64 years. One year and 10 months before admission this patient complained of substernal burning of 1 month's duration. A diagnosis of cardiospasm was made in another hospital.



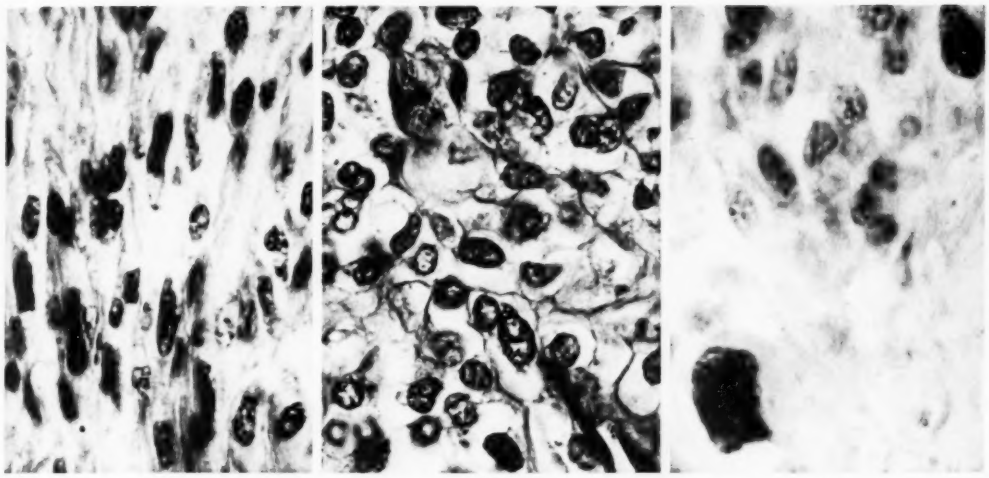
a b c

Fig. 2. a, Poorly differentiated tumor with rather uniform cellularity and absent giant cells—suggests medulloblastoma. Mallory's phosphotungstic acid hematoxylin stain. ×500. b, Characteristic pattern of polar spongioblastoma. Mallory's phosphotungstic acid hematoxylin stain. ×500. c, Large immature cells and one tumor giant cell typical of glioblastoma multiforme. Mallory's phosphotungstic acid hematoxylin stain. ×500.

This diagnosis was changed 3 months later to arteriosclerotic heart disease with coronary insufficiency and angina pectoris. He was given ½ grain of luminal 4 times daily and was free of symptoms 1 month later. Vision at that time was 20/20 corrected. His chief complaint was of a vermicular sensation over the right temple. He was seen at the Boston City Hospital for the first time 6 months before his final admission. He complained of bilateral supra-orbital pain, formication over the scalp, and a sensation of peculiar odors. Examination showed papilledema of 3 diopters but no localizing signs. A diagnosis of brain tumor—suspect of metastatic origin—was made. A month later his memory began to fail and he developed personality changes. He refused to permit adequate investigation at that time. On his final admission he was in deep coma. There was no history of injury or disease except as noted. On physical examination he showed a slightly enlarged heart, generally depressed tendon reflexes, left hemiparesis, and a choking of 4 diopters. He responded only to painful stimuli. His blood pressure was not recorded. Lumbar puncture showed an intracranial pressure of 140 millimeters of water. The cerebrospinal fluid was clear and colorless without cells and with a total protein of 103 milligrams per cent. A ventriculogram was done the day after admission. It showed a displacement of the anterior horns and the third ventricle to the left with dilatation on the left. The right ventricle was not entered with the needle, being overlaid by a cyst which then was visible as a separate structure in the right temporo-occipital region. The cyst fluid had a total protein of 5,580 milligrams per cent and the left ventricular fluid one of 47 milligrams per cent. A low right parieto-occipital craniotomy was performed at once. This revealed an extensive infiltrating tumor which lay astride the Sylvian fissure. On section, the tumor was found to be tough and had the appearance of a meningioma. A biopsy was done. The diagnosis from this tissue was reported as a malignant metastatic tumor, probably carcinoma, and with many mitoses. No further attempt at removal was made. The dura was closed tightly and the bone flap replaced. The patient did not regain consciousness and died 24 hours later. No autopsy was permitted.

Later and more detailed study of the biopsied tissue changed the original diagnosis. Microscopically, the tumor showed large areas in which the cells were well differentiated. The cytoplasm stained poorly, however, and the nuclei varied in shape from ovoid to spherical. Numerous intercellular neuroglial fibers were present. In such areas the tumor was considered to be growing as an astrocytoma, the tissue being similar to that shown in Figure 7a of Case 9. In other areas the picture was that of a polar spongioblastoma. The tumor cells were fusiform and had cytoplasm that stained fairly well. No intercellular fibrils were present. The appearance here was similar to that shown in Figure 1b, Case 2. In still other fields the cells were poorly differentiated, with tumor giant cells and moderate numbers of mitoses. We consider this appearance characteristic of a glioblastoma multiforme; shown in Figure 5c, Case 7.

Case 4 (N. S. 3035, A-38-483). Male, aged 64 years. Three months before entrance this patient began to have severe, throbbing, generalized headaches, shortly followed by repeated grand mal type of convulsive seizures. He had had 20 such during this period. Two weeks before admission his left side became weak. There was no other significant family or past history. On admission he was lethargic and somnolent with an evident memory defect. Physical examination was noncontributory except for the fact that he kept his head rotated to the right and that he had an enlarged boggy prostate. His blood pressure was 140/100 millimeters of mercury. He showed a left hemiparesis and hemi-hypesthesia with positive Babinski, Gordon and Oppenheim signs, the last being present on his right as well. The right disc was choked and the left could not be seen on account of lenticular opacities. There was a negative blood Hinton. Lumbar puncture showed an intracranial pressure of 350 millimeters of water with normal dynamics. The cerebrospinal fluid was clear, colorless, without cells and had a total protein of 102 milligrams per cent and a gold sol of 1122321000. Six days after admission, a ventriculogram was done. It showed a displacement of the ventricles to the left and in addition a shadow which looked like a separate lesion projecting into the lateral ventricle on the left. Fluid with a total protein of 6300 milligrams per cent was obtained from a cyst on the right at this time. The left ventricular fluid had 17 milligrams per cent of protein. A right posterior parietal craniotomy was done 2 days later. A soft subcortical vascular tumor was found in the temporoparietal region. The biopsied tissue was reported as having been identified as an astrocytoma. Excision was out of the question, on account of the tumor's size, so, after providing a small decompression, the rest of the dura was closed and the bone flap replaced. The patient died 48 hours later without regaining consciousness.



a b c

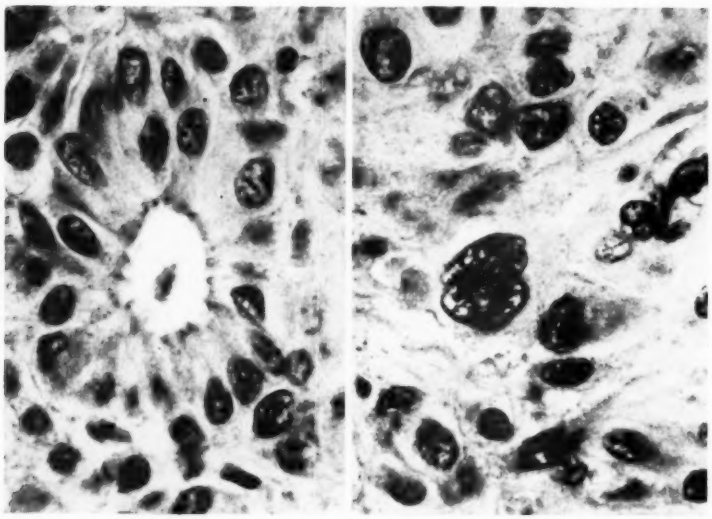
Fig. 3. a, Typical arrangement of cells of a polar spongioblastoma. Phloxine-methylene blue stain. ×745. b, Rather uniform cellularity with prominent cell margins and little intercellular substance. Strongly suggestive of oligodendroglioma. Phloxine-methylene blue stain. ×745. c, Tumor giant cell and undifferentiated cells characteristic of glioblastoma multiforme. Phloxine-methylene blue stain. ×745.

At autopsy the brain showed diffuse widening and flattening of the convolutions. In the right occipital pole there was a well circumscribed firm tumor measuring 4.0 centimeters in diameter. The center of the mass showed numerous cyst-like spaces measuring up to 2.0 millimeters in diameter and containing a light greenish yellow coagulum. In addition, in the superior portion of the right parietal lobe, there was a moderately firm, well circumscribed tumor measuring 1.3 centimeters in diameter.

Sections taken from the two tumors exhibited three types of glioma. In some fields the cells were fusiform with polar cytoplasmic processes. There were no intercellular fibrils. We may consider these areas as exhibiting the characteristics of a polar spongioblastoma (Fig. 2b). Another area exhibited poorly differentiated tumor cells whose cytoplasm stained very faintly. The nuclei were vesicular with prominent nucleoli. The nuclear shape varied from round to oval. There were no giant cells. Although for the greater part there was no characteristic arrangement, there was a suggestion of pseudo-rosette formation in a few instances. Intercellular fibrils were absent. We may consider this part of the tumor as a medulloblastoma (Fig. 2a). Associated with the regions appearing as polar spongioblastoma there were some areas showing larger cells than in either of the above. These cells showed poor differentiation and in some instances true tumor giant cells were encountered. We may consider these latter fields as exhibiting the criteria of glioblastoma multiforme (Fig. 2c).

CASE 5 (N. S. 3273, A-39-444). Male, aged 44 years This patient was known to have been a chronic alcoholic for a number of years, and he was believed to have had weakness of his legs for 5 years but more detailed information was lacking. He may have had a head injury 9 months previous to admission. Three months before admission, he was taken to another hospital during an alcoholic spree. While there, he developed bronchopneumonia and in the course of his stay was found to have had "marked generalized hyperreflexia; dysmetria; ataxia; sluggish pupils and bilateral choked discs." A lumbar puncture at that time showed an intracranial pressure of 500 milligrams of water. The cerebrospinal fluid was found to have had a total protein of 80 milligrams per cent. On this last admission, he was disoriented and ataxic and had noticeable weakness of his legs. Physical examination demonstrated atrophy of the muscles of his left arm, both shoulders, and both legs. His blood pressure was not recorded. He had bilateral high choked discs, nystagmus, dysmetria, and ataxia. He staggered and fell toward the left. There was marked weakness of the left hand. He had hyperactive tendon jerks, bilateral ankle clonus, and Babinski signs. The Weber test was lateralized to the right. Two days after admission, a ventricular estimation demonstrated a marked bilateral hydrocephalus with 10 and 9 milligrams per cent of protein in the right and left ventricular fluids, respectively. No air was put in the ventricles. Immediately following this procedure, a suboccipital craniotomy was started. It had to be abandoned after removal of the bone on account of excessive bleeding. The patient died without regaining consciousness about 8 hours later.

At autopsy, in addition to an intraventricular hemorrhage and bilateral bronchopneumonia, a tumor of the cerebellum and brain stem was found. The brain weighed 1,350 grams. A moderate cerebellar pressure cone was found. There was a moderately firm tumor lying beneath the pia arachnoid and involving the right cerebellar tonsil, brachium pontis, and the restiform body. The neoplasm measured 4 by 2 by



a b

Fig. 4. a. Gland-like arrangement of cells with blepharoplastin. This is characteristic of an ependymoma. Mallory's phosphotungstic acid hematoxylin stain. ×780. b, Poorly differentiated cells with a tumor giant cell. This is indicative of glioblastoma multiforme. Mallory's phosphotungstic acid hematoxylin stain. ×780.

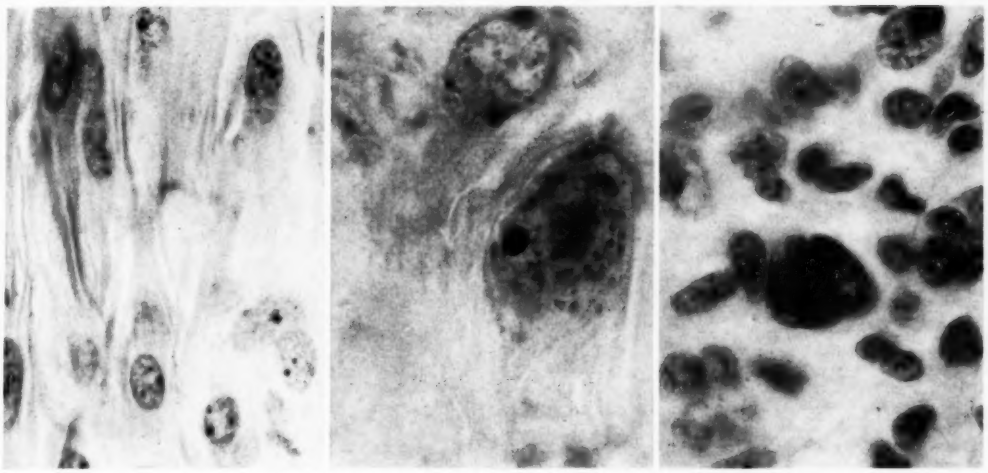
2 centimeters and on cut section revealed a nodular surface which for the greater part showed a light yellowish gray color in which were smaller, light brown areas measuring up to 0.5 centimeter in diameter. There was moderate dilatation of the lateral ventricles.

Microscopically, the tumor exhibited considerable variation in appearance from field to field. In some areas the tumor had the appearance of a polar spongioblastoma, the cells being of moderate size and spindle-shaped (Fig. 3a). Intercellular fibrils were absent. In still other fields there were sheets of tumor cells with prominent cell margins which gave them the appearance of an oligodendroglioma (Fig. 3b). In other areas there was the haphazard cellular arrangement with tumor giant cells that is indicative of glioblastoma multiforme (Fig. 3c).

Four other tumors had, in addition to the glioblastomatous, ependymomatous tissue (twice) and astroblastomatous or astrocytomatous sections once each.

Case 6 (N. S. 2586, S-39-3004). Male, aged 13. This patient was well until January, 1937. At that time he suddenly developed diplopia. Two months later he had severe frontal headache accompanied by nausea and vomiting. Four months later he was first admitted to the hospital. He had had no previous history of injury or other significant illness. Glasses had relieved his headaches before admission but transitory attacks of diplopia persisted. Physical examination revealed a well developed and nourished boy of 13 years. His genitalia were small, and the right testicle was undescended. He was co-operative and oriented, conscious and rational. There was a weakness of the left external rectus muscle and of the left side of the face of a central type. The discs were markedly choked and exudate was present. There was a right homonomous hemianopsia. His tongue deviated to the right. The tendon reflexes were all markedly depressed or absent. There were bilateral Babinski and Chaddock signs. His blood pressure was not recorded. His pulse, temperature and respirations were all normal. There was noticeable clumsiness of both hands. A lumbar puncture showed an intracranial pressure of 350 milligrams of water. The cerebrospinal fluid was clear and colorless with a total protein of 43 milligrams per cent. The rest of the laboratory tests were normal. A diagnosis was made of a left cerebral tumor, and a left posterior parietal craniotomy was performed. A large cyst was tapped in the lower parietal area. This was opened and drained after which a large bluish red, vascular and cellular tumor was found on its medial wall. A piece was removed and examined microscopically. As a result, it was reported to be an ependymoma. Further exploration demonstrated that the tumor had invaded the wall and partly filled the cavity of the lateral ventricle. It was very vascular and so was left intact except for the biopsy. A decompression was provided, and the bone flap replaced. After a stormy convalescence he was discharged to his home. At that time he was aphasic, had a bilateral motor weakness and unsteady gait. The choking had disappeared and the visual fields, especially that on the left, were noticeably improved.

For a year and one-half he continued to improve and became practically normally active. At the end of that time he had his first convulsive attack. Fight months later, having completed, at home, the work done in public schools by a boy of his age, he again had diplopia and early choking of his discs was again discerned for the first time.



a b c

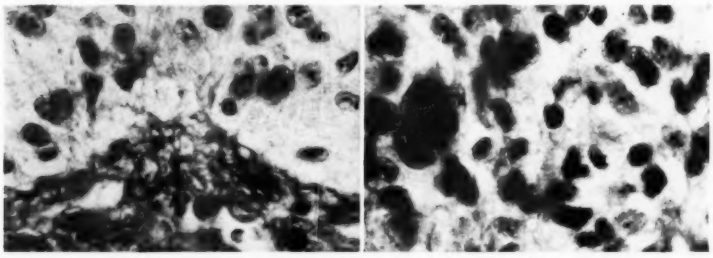
Fig. 5. a, Large spindle cells arranged in a palisade formation with coarse intercellular fibrils. Suggestive of ependymoma. Mallory's phosphotungstic acid hematoxylin stain. ×745. b, Numerous intraprotoplasmic and blepharoplastin granules. These cells establish the diagnosis of ependymoma. Mallory's phosphotungstic acid hematoxylin stain. ×1490. c, Haphazard cellular arrangement with tumor giant cells. This is characteristic of glioblastoma multiforme. Mallory's phosphotungstic acid hematoxylin stain. ×745.

He was given x-ray therapy and 2 months later was improved. One month after completion of a series of 20 treatments, he was readmitted to the hospital because of increasing drowsiness to coma for the previous 24 hours. This was 2 years and 9 months after the onset of his symptoms and 2 years and 3 months after his operation. He had all the signs of increased intracranial pressure. The right ventricle and the cyst on the left were emptied through the old trephine holes as an emergency measure and 19 days later the old craniotomy wound was reopened. A radical resection of the tumor that now filled the ventricle and invaded large areas of the parietal and temporal lobes was done. Many cysts were encountered, much tissue was soft enough to suck out, and much was very firm and fibrous and had to be removed by sharp dissection. He had a stormy convalescence with severe headaches, a right hemiparesis, and profound aphasia. During his hospital stay he was given another series of x-ray treatments and eventually was sent home 2 months after admission, able to speak normally, without choked discs, and active all day with the aid of a cane and an orthopedic brace to control his foot drop. He still had a right homonomous hemianopsia. He has continued to improve during the succeeding 6 months to date.

A complete histological study was carried out on the tissue that was removed at the last operation. It was composed, in gross, of many pieces of friable gray tissue, the aggregate mass measuring 3.0 cm. in diameter.

Microscopically, some regions of the tumor showed fairly well differentiated cells. In some instances these were columnar in shape and assumed gland-like formation. The cytoplasm beneath the margin of the gland-like spaces contained moderate numbers of dipharoplastin granules (Fig. 4a). These areas were considered characteristic of ependymoma. In other areas the tumor appeared as a glioblastoma multiforme with lack of cell uniformity and the presence of multinucleated tumor giant cells (Fig. 4b).

CASE 7 (N. S. 2950, S-38-1696). Male, aged 53 years. This patient had been entirely well up to 2 weeks before his admission. At that time he had "bumped his head" without unconsciousness or other immediate symptoms. Frontal headaches developed for which he consulted his local doctor and was told that he had "sinusitis." For the week previous to admission he was unable to read and was "out of his mind." On admission he was completely aphasic, disoriented, and confused but co-operative. Physical examination showed moderate arteriosclerosis, bilateral high choked discs, righ homonomous hemianopsia with sparing of the maculae, dilated fixed pupils, alexia, and partial sensory and motor aphasia. There was no astereognosis. The patient was right handed. The tendon reflexes were within normal limits, and there were no abnormal reflexes. He had a high intracranial pressure (230 mm. water) with cerebrospinal fluid that was clear, colorless, without cells, and with a total protein of 70 milligrams per cent. Serological tests were all negative. His blood pressure was 128/70 millimeters of mercury. Two weeks after admission a left temporoparietal craniotomy was performed. A large, soft infiltrating cystic tumor of the temporal lobe was widely removed. Microscopic diagnosis at the time of the operation was glioblastoma multiforme. A decompression was provided, and the bone flap was replaced. He made a satisfactory convalescence and returned home 2 weeks after the operation with a normal intracranial pressure but with all his other symptoms and signs just as they were before operation. During the succeeding 6 months at home he gradually went down-hill and after a week of unconsciousness, died 8 months after he had noticed his first symptom. There was no autopsy.



a b

Fig. 6. a, Pyramidal shaped cells with sucker-feet attached to the wall of a blood vessel. This is characteristic of an astroblastoma. Mallory's phosphotungstic acid hematoxylin stain. ×555. b, Haphazard cellular arrangement with a tumor giant cell. This is characteristic of glioblastoma multiforme. Mallory's phosphotungstic acid hematoxylin stain. ×555.

A complete histological examination was carried out on the tissue removed at operation. This was in the form of several fragments of firm to gritty grayish white tissue, the largest measuring 2.0 centimeters in diameter; the smallest, 0.4 centimeters.

In some microscopic fields the tumor cells were elongated, fleshy and arranged in palisade formation. There were coarse intercellular fibrils (Fig. 5a). Some cells exhibited numerous blepharoplastin granules in their cytoplasm thus establishing the diagnosis of ependymoma (Fig. 5b). In other fields there was no orderly cellular arrangement nor any intercellular fibrils. Mitotic figures were numerous and tumor giant cells were present in moderate numbers. We classify the tumor in these fields as glioblastome multiforme (Fig. 5c).

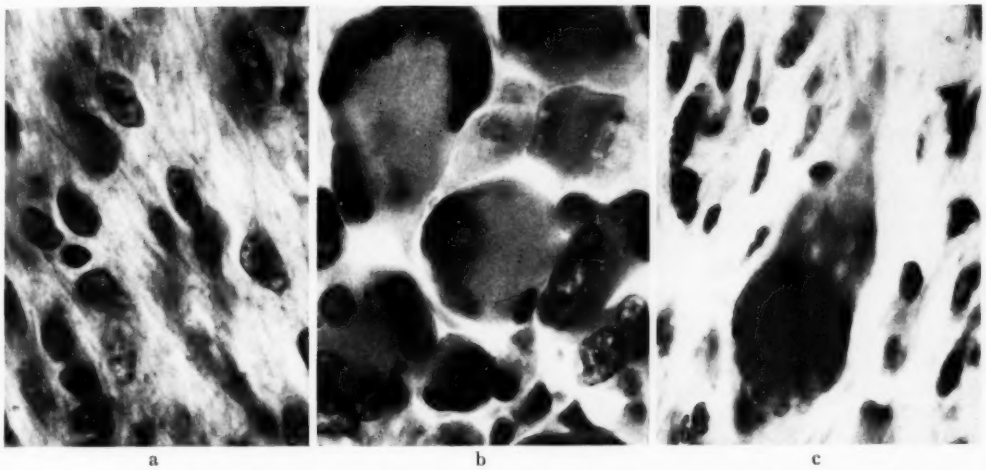
CASE 8 (N. S. 2989, S-38-2706). Female, aged 29 years. For 5 months before admission, this patient had been having left frontal headaches and increasing somnolence. At the time she first noted these symptoms, she was 2 months pregnant. Two months before admission, she fell. Following that she began to act abnormally, talked out of one side of her mouth, and developed weakness of her left hand. Having always been left-handed she now began to use her right hand almost exclusively. Her left leg, face, and shoulder progressively became weaker until she had a complete left hemiplegia. For a month before admission, she had a moderate aphasia and for a week she had been vomiting and complained of loss of sight in her left eye. On admission, she was stuporous and restless. She had had no significant previous illnesses or injuries. Physical examination demonstrated that she was 8 months pregnant, had a left hemiplegia, astereognosis on the left and aphasia. Her blood pressure was not recorded. At lumbar puncture she was shown to have an intracranial pressure of 220 millimeters of water. The cerebrospinal fluid was clear, colorless, without cells and had a total protein of 86 milligrams per cent. Blood and cerebrospinal fluid Wassermann and Hinton test were negative. She showed a trace of sugar but no albumen in two urine examinations. She had a secondary anemia. Two weeks after admission she was delivered of a live baby by cesarean section. The baby, however, died in a few days of hemorrhagic disease of the newborn. The mother's convalescence was uneventful.

Three weeks after the cesarean section, a ventriculogram showed the right lateral ventricle to be compressed with both ventricles displaced to the left and a large cyst in the middle region of the right cerebral hemisphere. The left ventricular fluid had a total protein of 11 milligrams per cent and the cyst one of 4,680 milligrams per cent. The following day a right posterior parietotemporal craniotomy was done. The subcortical cyst was opened just above the supramarginal gyrus, and tumor tissue was demonstrated posterior and superior to it. Microscopic examination of a biopsied specimen of this tissue was reported as showing a rapidly growing astrocytoma. This cyst wall was destroyed and a small amount of tumor removed. It proved to be impossible to replace the bone flap, so it was sacrificed, the dura being closed except on the posterior inferior margin. After a stormy convalescence complicated by a cerebrospinal fluid fistula through the scalp wound, she got up and about the ward actively and was allowed to return home 3 months after admission. There was considerable bulging of the decompressed area.

For 11 months she was comfortable and moderately active about her home. She had no symptoms and was bothered only by the increasing size of the decompression. At this time she began to be disabled by an increasing hemiplegia and hemianopsia. Her blood pressure was 140/84 millimeters of mercury. She was readmitted for possible re-operation. This was attempted but had to be abandoned on account of excessive bleeding. The wound failed to heal, a fungus developed, she became weaker, irrational and confused, and eventually died 4 months later, 1 year and 10 months after her first symptoms and 1 year and 2 months after her first operation. There was no autopsy.

The tissue removed at the first operation was subjected to a later more detailed study. It was an egg-shaped mass measuring 5.5 by 3 by 2.5 centimeters. The tissue cut with moderate resistance and the cut surface presented alternating areas of white, lemon yellow, and black.

Microscopically the tumor was largely composed of cells whose nuclei were fairly vesicular and cytoplasm indistinct. Intercellular fibrils were absent. About blood vessels the tumor cells appeared fusiform with fairly well defined sucker-feet attached to the adventitia. This part of the



a b c

Fig. 7. a, Well differentiated cells with numerous neuroglial fibrils. This is characteristic of an astrocytoma. Hematoxylin and eosin stain. ×745. b, Huge giant cells somewhat resembling foreign body giant cells. These probably represent multinucleated astrocytes. Hematoxylin and eosin stain. ×745. c, Large tumor giant cell establishing the diagnosis of glioblastoma multiforme. Hematoxylin and eosin stain. ×745.

tumor was considered to be an astroblastoma (Fig. 6a). In other scattered fields mitotic figures were fairly numerous and occasional tumor giant cells were found. This tissue we consider typical of glioblastoma multiforme (Fig. 6b).

CASE 9 (Private, S-38-1967). Male, aged 67 years. This patient had been well and active until 9 months before admission. At that time he was injured in an automobile accident, having been struck on the right temple. He was unconscious for a short period. He remained active in business for 7 months after although it was noted that during that time he became more and more irritable and forgetful and was easily depressed and fatigued. At this time he first complained of "stiffness" of the left hand and arm, to which a sense of numbness and awkwardness was added after he had been curling on one occasion. Ten days before admission he had a convulsive seizure involving his left hand, arm and face without loss of consciousness. This was repeated at intervals until admission. The attacks were preceded by parasthesias in the same distribution. Physical examination showed normal eye grounds, obesity, arteriosclerosis and a flaccid paralysis of the left hand and arm with absent tendon reflexes. There were increased knee and ankle jerks with the left greater than the right, slight bilateral ankle clonus and no abnormal reflexes. There was a left hypesthesia. His heart was enlarged to the left and there were some moist râles at the bases of his lungs. His blood pressure was 180/100 millimeters of mercury. At lumbar puncture, an intracranial pressure of 190 millimeters of water was demonstrated. The cerebrospinal fluid was clear, colorless, had 3 lymphocytes and a total protein of 45 milligrams per cent. Roentgenograms of the skull showed the pineal gland in normal position. A diagnosis of cerebral subdural hematoma suspect was made, and 2 weeks after admission a right transtemporal exploratory trephination was done. It was noted that the temporal lobe was softer to palpation than the rest of the brain, and after removal of about 30 centimeters of fluid that was thought to be but could not be proved to be subdural fluid, the brain fell away about ¾ inch from the under surface of the dura. The dura was left open and the wound was closed about a drain which was removed 24 hours later. The fluid collected at operation proved to have a total protein of 45 milligrams per cent. The operation made no change in his symptoms or signs. He gradually grew weaker and more confused, had an occasional generalized convulsive seizure and died 5 weeks after operation after a short period of unconsciousness.

At autopsy, the brain showed an extensively infiltrating tumor involving the right frontal and parietal lobes.

The microscopic sections showed considerable variation in appearance with the tumor growing fundamentally as an astrocytoma and as a glioblastoma multiforme. In some areas the cells were well differentiated although their cytoplasm stained poorly if at all, and there was an abundance of intercellular fibrillar substance (Fig. 7a). A number of fields showed numerous giant cells which appeared to be of two types, one of which showed considerable cytoplasm with a rim of well differentiated and relatively small nuclei. These cells had some similarity to foreign body giant cells as seen outside the central nervous system and probably represented the giant astrocytes described by Penfield (Fig. 7b). These findings were considered typical of an astrocytoma. Other giant cells showed a relatively small amount of cytoplasm and large irregular nuclei, a picture characteristic of tumor giant cells (Fig. 7c). These cells were associated with a moderate number of mitoses. This picture was consistent with the diagnosis of glioblastoma multiforme.

If Bailey and Cushing's theory of progressive cellular age in the development of gliomas is correct, it will be evident that the combinations here described not only bring together in one mass cells at opposite ends of a single family tree, but also cells from two entirely discreet families. No explanation is offered to account for this bizarre cellular grouping. It is merely recorded in the hope and expectation that it, together with other similar observations, will eventually help to clarify the glioma problem.

In the meantime and from the clinical point of view, the malignancy of glioblastomas, the benignancy of astrocytomas, and the appropriate varying degrees of malignancy of the intervening tumors must be accepted as the present foundation on which to build surgical therapy. Even this statement must be regarded as only temporary, however. Scherer, in an article entitled "The Forms of Growth in Gliomas and Their Practical Significance" presents conflicting evidence which, if confirmed, may be taken as demonstrating that a considerable percentage of glioblastomas are therapeutically favorable and that all astrocytomas are invariably therapeutically unfavorable tumors. Lacking such confirmation, it is better for the present to adhere to the more orthodox and older beliefs. From this point of view, the potential inaccuracy of the biopsy diagnoses made at the time of the operation in this series is striking. There was a failure to identify histologically at this time, the presence of the most unfavorable type of tumor cell in 4 of 6 cases, and in only 1 case was the co-existence of the more benign cells accurately recognized. In 2 other instances, the presence of a tumor was not even suspected even though one patient was explored in the attempt to make a diagnosis. In the remaining patient, a pre-operative diagnosis of neoplasm was made but the tumor could not be exposed on account of the man's condition.

Little help in detecting the type of tumor was had from the history and examination. Of the two the history was probably of greatest significance. The one cerebellar tumor caused recognizable symptoms for 5 years before the patient consulted a physician about them. However, the patient suffered from chronic alcoholism for which he was hospitalized several times. At his final admission he was in coma and the history was obtainable only from friends and previous hospital records. In no other instance did this period exceed 6 months and in one the patient himself repeatedly stated before and after the diagnosis had been made that his symptoms preceded his hospitalization by only 2 weeks. In 1 case hospitalization was brought about because of an acute exacerbation of previously negligible symptoms by pregnancy. A living 8 months baby was delivered by cesarean section but it died of hemorrhagic disease in a few days. One month later, subtotal resection of mother's tumor was done.

The location of the cerebral tumors was also without diagnostic or prognostic significance.

The postoperative survival period was of no significance. It was conditioned by such uncontrollable factors as previous alcoholism, inadequate food, pregnancy, syphilis, age, misleading history, the presence of a cyst in the tumor, and so forth. The only patient with a significant survival period is one that had a combined glioblastoma and ependymoma which was partly intraventricular. He is still living at the age of 16, 3 years after his first operation. One of the 2 correctly diagnosed cases, as far as the glioblastomatous part went, lived 6 months and the other 9 days after operation. Only a small biopsy was done in the latter. One patient with a tumor that was partly glioblastomatous and partly astroblastomatous lived 14 months and another with a tumor that was partly astrocytomatous lived 5 weeks. The former had a subtotal resection and removal of the bone flap at her first operation followed by repeated tappings of a cyst and 2 secondary operations. The latter did not even have his tumor exposed. Four tumors were cystic in part, the rest being completely solid. Two cases died because of peripheral circulatory failure 48 hours and 14 months after the first operation. One died because of a ventricular hemorrhage 12 hours after operation, in one the cause of death was not determined and the remaining patients died of massive cerebral edema with a cerebellar cone, from a few hours to 9 days after operation.

Failure to make a correct histological diagnosis of the tumor at the time of operation was due to one chief factor. In this connection, it is obvious that those cases in which the tumor was not seen because of no or inadequate operative exposure can be eliminated. With these eliminated there are 3 tumors which were classified from material removed at operation only, and 3 in which postmortem studies were made in addition. Regardless of anything else, the important datum to obtain at the earliest possible moment about any intracranial tumor is whether or not it is wholly or partly made up of malignant glioblastomatous or medulloblastomatous tissue. As a corollary to this, care must be taken, of course, not to confuse the "giant astrocytes" described by Penfield as occurring in astrocytomas (Fig. 7b), with the true tumor giant

cells that characterize the glioblastomas. Thus, the ultimate measure of success that attends any attempt at classifying histologically a given tumor rests on the ability of the pathologist to recognize, while the operative field is exposed, the presence of either one of these 2 cell groups regardless of whether or not any other less malignant cell group is identified at the same time. In the 6 cases in which surgically removed tissue was available, this requirement was met twice. Immediate diagnoses were made from tissue obtained by small biopsies in 3 and by subtotal excisions in 3. Glioblastomatous tissue was recognized once in each group. It is fair to conclude, despite the small size of the group and because of a 66 per cent error, that accurate operative histology requires more tissue than is obtainable from any removal smaller than that of a wide spread excision. All these first diagnoses (made while the patient was being operated upon) were made on fresh tissue examined either after supravital staining of a smear or after frozen section, or both. That the dual nature of these tumors was not recognized at this time was due partly to the concentration of the pathologist on making a single definite cellular diagnosis but chiefly to the small amount of tissue that was provided him. It was not until after more material was obtained by autopsy or a more prolonged study of a greater number of fixed sections made that the multiplicity of types was recognized. It seems reasonable to conclude therefore, that the accuracy of the histological classification of an intracranial glioma, even if not extended beyond the point where the only requirement shall be a certain recognition of the presence of glioblastomatous and medulloblastomatous tissues, increases directly with the amount of tumor tissue made available by the surgeon and studied by the pathologist.

SUMMARY

The classification of intracranial gliomatous tumors as proposed by Bailey and Cushing cannot by considered satisfactory or final at this time. If adhered to, it has been found possible to demonstrate in individual tumors cells from either extreme of a given family tree or from different families altogether. In the absence of any classification as good however, it is preferable to use it at this time and, as a result, to consider the glioblastoma and medulloblastoma as histologically the most malignant and unfavorable types and the astrocytoma and ependymoma as the most benign and favorable types of the common intracranial gliomas. On that basis, it must be conceded that the therapy and prognosis of any given intracranial glioma will depend on the ability of the pathologist to recognize in biopsied specimens and during the operative procedure, the presence of glioblastomatous or medulloblastomatous tissue, more accurate classification being reserved for later study. Furthermore, it appears probable that any intracranial glioma that contains either of these two cell groups has, for practical purposes, a life expectancy of about a year and that the operative risks must be assayed accordingly. Such risks should include not only the chances of death on the table but the even more important chances of life with complete disablement. The accuracy of the pathologist's diagnosis and therefore the amount and efficiency of the surgeon's therapy varies directly with the amount of tumor tissue available to and studied by the former at the time of the operation.

CONCLUSIONS

About 11 per cent of intracranial gliomatous tumors are of truly mixed type.

A patient with an intracranial gliomatous tumor, as far as we know now, that contains either glioblastomatous or medulloblastomatous tissue will have, with only rare exceptions, a life expectancy of not more than about 1 year.

Surgeons should not expect and pathologists should not give an opinion as to the degree of malignancy of a given intracranial glioma without the proviso that its accuracy varies directly with the amount of tissue provided by the one and studied by the other.

Surgical therapy of intracranial gliomatous tumors should be conditioned as much by the demonstration by the pathologist during operation, of glioblastomatous and medulloblastomatous tissue, as by the accessibility of the tumor that is to be removed.

We wish to thank Drs. Leslie S. Jolliffe and G. Kenneth Mallory, both of the Mallory Institute of Pathology of the Boston City Hospital, for preparing the photomicrographs.

BIBLIOGRAPHY

1. BAILEY, PERCIVAL. Intracranial Tumors. Pp. 216 *et seq.* Springfield, Illinois: Charles Thomas, 1933.
2. CARMICHAEL, E. A. Cerebral gliomata. J. Path. & Bacteriol., 1928, 31: 493.
3. GLOBUS, J. H. Die Umwandlung gutartiger Gliome in boesartige Spongioblastome. Ein Beitrag zur Frage der gliogenen Geschwuelste des Nervensystems. Ztschr. f. d. ges. Neurol. u. Psychiat., 1931, 134: 325.
4. GLOBUS, J. H., and STRAUSS, I. Spongioblastoma multiforme, etc. Arch. Neurol. & Psychiat., 1925, 14: 139.
5. LEVINE, G. Some transitional gliomas. Am. J. Cancer, 1939, 35: 22–37.
6. PENFIELD, W. Classification of gliomas and neuroglia cell types. Arch. Neurol. & Psychiat., 1931, 26: 745.
7. SCHERER, H. J. The forms of growth in gliomas and their practical significance. Brain, 1940, 63: 1: 1.

JUVENILE KYPHOSIS

JOHN T. HODGEN, M.D., F.A.C.S., and CHARLES H. FRANTZ, M.D., F.A.C.S.,
Grand Rapids, Michigan

THE orthopedist constantly sees children with rounded shoulders and poor posture. Quite often a patient is presented by the parent seeking advice for one of two reasons—posture or pain and fatigue. Ache and fatigue in children between the ages of 10 and 17 years, when present in the dorsal spine, demand careful investigation. For a number of years the hollow-rounded back of adolescents has interested us.

The clinical condition of juvenile kyphosis is not as rare a disease as formerly thought. In the last two decades the literature has grown to quite a volume, the majority of contributions having appeared in foreign publications.

Schanz first suspected that posterior curvature developing in children did not wholly arise from poor posture in school, but had a more serious background. He believed the kyphosis of adolescents was the result of heavy work and unusual demands on the back. Scheurmann, in 1921, described the term kyphosis dorsalis juvenilis, publishing his clinical and roentgen interpretations of the irregular outlines of the vertebral bodies. Schmorl, in numerous publications of his anatomical and pathological studies, has given us his conception of the vertebral changes. Haas in the past year has added pertinent studies in regard to growth of the vertebral column and epiphyseal changes resulting from injury.

For the past 6 years particular attention has been paid to children with dorsal back pain and kyphosis. They have been followed carefully and the treatment has been supervised as closely as possible under the orthopedic department.

It is our purpose in this presentation to review briefly the clinical picture of juvenile kyphosis, speculations as to etiology, pathology, and treatment with a few personal additions in the management, which we believe have been an aid in handling these children.

ETIOLOGY AND INCIDENCE

Many hypotheses regarding etiology have been advanced; what the true etiological factors are, however, is impossible to state definitely. The problem of balance between the capacity of the spine and functional demand is an important factor, in each individual case. The use of the term "functional demand" is based on the evaluation of physical demands made on the individual in relation to the economic status of the home, number of children in the family, rural or urban environment, physical work, labor laws, and educational demands. The capacity of the spine implies tolerance to physical exertion at any stage in its development and must include the factors of growth, diet, and protoplasm.

From a clinical standpoint four possibilities present themselves: (1) abnormal functional demand plus normal back—juvenile kyphosis; (2) abnormal functional demand plus abnormal back—juvenile kyphosis; (3) normal functional demand plus normal back—0; (4) normal functional demand plus abnormal back—juvenile kyphosis.

Statements one and two seem self-explanatory if one accepts developmental defects such as malformations of the vertebral body, malposition of notochordal structures, and endocrine disturbances. Schmorl is of the opinion that there are abnormalities not evident, particularly in the cartilaginous stage of development which, under stress and strain of greater functional demand, become clinically pathological. Statement three must be considered as a possibility. However, with no abnormal elements present a pathological picture can hardly be expected to develop. Statement four is a combination of factors which we believe may produce the clinical entity. This patient is a small part of the group and usually presents no pain, ache, or fatigue. Posture only is poor. These children appear in the non-indigent class and no abnormal demands could be determined during the daily routine.

From a study of 50 cases, the most frequent age of onset was found to be between 10 and 11 years (Fig. 1). Contrary to some observers, the incidence was found to be greater in girls (78 per cent). This observation coincides with the predominance of females as recorded by Burns and Ellis in the Royal National Orthopaedic Hospital and with the figures of Schuldbach of Leipzig. The incidence peak is highest earlier in girls, being reached at 10 years and in boys 11 to 14 years. In appraising the body types of these children it was found that the tall, thin child of the asthenic constitution appeared twice as frequent as the short stocky pyknic individual (Fig. 2). The

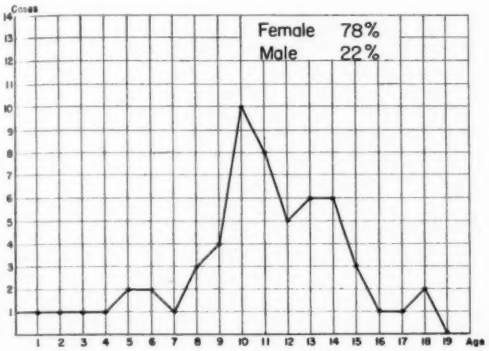


Fig. 1. Incidence.

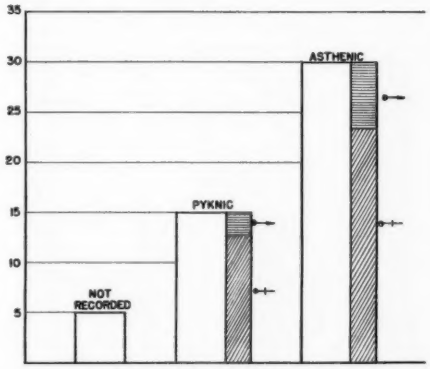


Fig. 2. Constitutional type.

majority of patients presented themselves under 6 months after the onset of symptoms—smaller groups sought advice from a year to 18 months following initial symptoms (Fig. 3). From the time element it would appear that the symptomatology in these children is not alarming nor is it of a severe nature in regard to pain or acute discomfort.

PATHOLOGY

Prior to anatomical investigations, the changes of the vertebral column in juvenile kyphosis were largely interpreted from the roentgenogram. Scheurmann in 1921 described the changes in adolescent spines from the roentgenogram, pointing out the increased dorsal curve and wedging of the body. Shanz before him speculated on the factors back of these changes early in 1907.

Numerous publications by Frejka, Mau, Calve and Galland, and Meyer described the clinical picture and development of deformity. All these authors turned in part to Schmorl's anatomical dissections and Scheurmann's interpretations for explanation of the changes occurring within the disc and vertebral body. These investigators carried out extensive studies of the spine and came to definite conclusions as to the development of the pathological picture. Schmorl's theory propounds the herniation of the nucleus pulposus into the vertebral body causing reactive changes and cessation of bone growth. Scheurmann believed the primary change not a nuclear herniation but erosion of the anterior corners of the bodies, and also states that nuclear herniations are not always present. Cloward and Bucy reviewed cases of extradural cysts of the cord in which kyphosis was present. These cases occurred in children, and so consistent were the findings that coincidence appeared out of the question. The explanations offered in relationship of the cysts to development of kyphosis may spread some light for future investigation. Their theory states that venous stasis and congestion within the ventral body may be a contributing factor. All these writers have attempted reasonable explanations for the changes, but there still remains much controversy. One cannot possibly outline the various individual conceptions in this short review; however, the general conception of the changes can be sketched here.

Anatomically, the intervertebral disc consists of three distinct parts; the annulus fibrosa, the nucleus pulposus, and the two cartilaginous end plates which form the inferior and superior coats of the disc.

The annulus is a fine fibrous network running in oblique planes covering the anterior lateral and posterior borders of the discs. It completely encircles the intervertebral disc substance and is

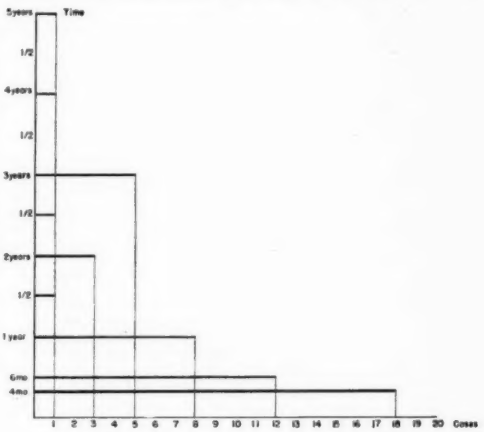


Fig. 3. Duration symptoms prior to treatment.

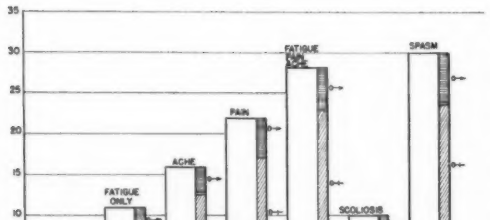


Fig. 4. Symptoms and signs.

attached more loosely in the dorsal or posterior aspect. The peripheral edges of the annulus send fibers deep into the marginal ledges of the vertebral body. The fibrous networks of the annulus pass gradually centralward becoming less dense and less compact, gradually merging into the nucleus pulposus which is partly myxomatous and partly fibrillar. In youth the pressure within this structure is greater than in the aged. Petter found that, on removal from the body, the intervertebral disc expands and a pressure of some 30 pounds is necessary to reduce this expansion. Evidently this pressure is due in part to water content. In the youth there exists 80 parts of fluid as in contrast to the aged where only 69 parts fluid is present.

The cartilage end plates are thin rigid structures of hyaline cartilage forming the superior and inferior surfaces of the disc. They do not reach the outer visible margin of the disc but end on the inner marginal ledge of the corona, which will be mentioned below.

The tension within the nucleus is maintained by the lamina and cartilage end plates. Schmorl removed a bony vertebral body from the disc being careful not to injure the cartilaginous end plate and found that the tension within the intervertebral disc did not change. He concluded, therefore, that the cartilaginous end plates must be an important factor in maintaining tension. Evidently then, the cartilage plate is as intimate with the disc as with the vertebral body.

If for some reason the resistance of the cartilaginous end plate is below normal, changes in tension may occur by herniation of nuclear tissue through small splits in this end plate. Whether these fissures or interstices develop from strain or trauma, or weakened areas exist as the result of involuted nutrient vessels from an earlier age, cannot definitely be stated. The abnormalities may remain within the bounds of clinical normalcy and assume a pathological character only under the stress and strain of increased functional demand on the disc. It is from this basis that we mentioned the four statements or combinations possible in developing the clinical entity.

It is believed that under increased demand zigzag fissures appear in the cartilaginous plates, allowing nuclear material to herniate into the spongiosa of the vertebral body. The pressure of the nuclear substance further tears and enlarges the fissures allowing a greater mass to come through. Reactive changes develop around these cartilage nodules in the spongiosa of the vertebral body. By release of tension the width of the intervertebral disc is lessened and the cartilaginous plates approach each other. In areas in which the perforations occur through the bony end plates of the vertebral body, the cartilage proliferation zone is destroyed and bone growth ceases. This is the case at the ventral or anterior portion of the vertebral body when greater pressure is exerted.

The delay in growth is shown as narrowing of the anterior body producing the picture of wedging. Defects in the ossification are seen along with irregular broadening of the cartilaginous proliferation zone.

Schmorl apparently objects to the term vertebral epiphysis as used by Scheurmann in designating the ossification line as an epiphyseal line. He stated, and was supported by Virchow, that the so called secondary epiphysis is not a growth epiphysis in the same sense as a long bone. The vertebral body develops by endochondral bone growth on the spongiosa side of the cartilage end plates. One may be justified in speaking of this as a *growth* zone and not an epiphysis, thus, discarding the term vertebral epiphysitis. Haas, however, in experimentation on dogs concluded that the growth in length of vertebrae occurs in a manner similar to growth in length of long bones, a proliferation at the cartilage end plate with no interstitial growth within the body. He produced both kyphosis and scoliosis by injuring these plates surgically. These variants in conception of growth do not change the ultimate result. The nuclear substance under pressure, whether destroying the cartilage proliferation zone of Schmorl or the cartilaginous epiphyseal cells according to Haas, interrupts the growth anteriorly to produce wedging or lateral changes may produce a scoliosis.

Frejka seems to stress the possibility of nasal obstruction playing an important rôle in the development of kyphosis. Children with large adenoids and tonsils breathe through the mouth, such respiration is shallow and there is a more or less constant condition of expiration in the thorax. A

constant condition of this description causes a change in posture and in the general form of the spine and thorax. The chest is dropped and slumping occurs. The increased curving of the dorsal spine increases pressure within the discs.

In the near past roentgenologists frequently assumed that a disease of the epiphysis existed because this area was seen as a hazy and indistinct or irregular outline. These areas may be interpreted as irregularities in ossification interrupted by passage of nuclear substance through the end plate into spongiosa.

In the adolescent spine one finds about the periphery of the bony end plate, a cartilaginous ring. During the period of growth small areas of calcification or ossification appear within this ring and as time goes on these areas become confluent finally to present a bony ring. This ossifying or calcifying ring may be seen roentgenologically in its different stages of development. This picture will be referred to later in conjunction with roentgen diagnosis.

In brief summary of the development of these changes one may say that the destruction of the growth zone or epiphyseal cartilage zone may be caused by herniations of the intervertebral disc with resultant decrease in growth anteriorly in the vertebral body. While we have seen clinical kyphosis in the adolescent without radiological evidence of nuclear prolapse and again multiple nuclear herniations without kyphosis, we are sure that the nuclear herniations and cessation of growth of the body anteriorly are important considerations in the development of juvenile kyphosis.

CLINICAL PICTURE

Patients presenting themselves for examination do so usually for two reasons, poor posture or ache and pain in the back. A slumping posture has been noticed for a number of months and the child has complained of backache. On the other hand, the parent suddenly discovers the child has a badly rounded back and seems easily to become fatigued.

Ache or pain with fatigue are present in the majority of cases (Fig. 4). It is this symptom which brings attention to the back even in absence of curvature. The individual has a dull aching in the mid dorsal or low dorsal region, the severity of which may vary from a feeling of fatigue to aching and actual radiating pain on exertion. At times, the complaint of chest pains may be elicited with a "crowded" sensation in the thoracic cage. Many times the child is content to come straight home from school and rest at his own initiative rather than run and play after school hours. This act of voluntary rest points to fatigue and is present at times without evident postural changes in the dorsal spine.

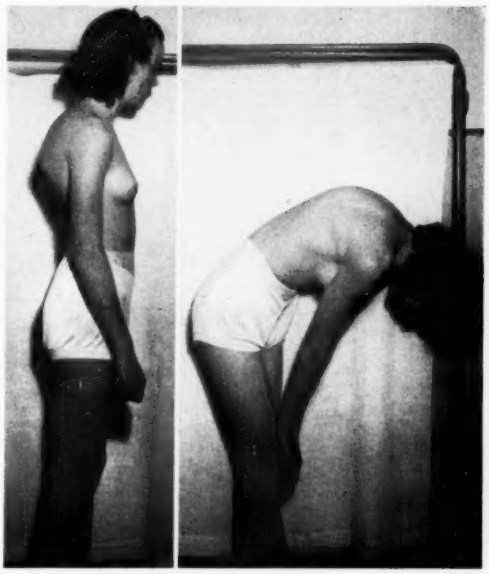


Fig. 5. a, left. Shows posture with increased curve dorsal spine. Head carried forward. b, Shows in forward bend the arcuate curve in mid and high dorsal spine.

A greater percentage of children with back complaints are of the tall, ungainly type (Fig. 2). They have "sprung up overnight" so to speak in their growth. It has been our experience that these children complain of aching more than fatigue.

On examination one observes a rounded back accentuated by a slump of the shoulders. The head is carried forward, thus accentuating the contour of the dorsal spine. The chest is more or less flattened and plays a minor part in breathing. The abdomen is relaxed and abdominal breathing is pronounced. This picture is more in evidence in the tall individual (Figs. 5a and b). Increased lumbar lordosis in association with hyperextension of the knees and pronated feet completes the picture.

Palpating the dorsal spine one seldom elicits localized areas of pain or tenderness. Sharp tapping over the low dorsal spine with the heel of the hand may cause the patient to complain of pain especially in the forward bend position. The erector spinae group may exhibit spasm in the lumbar and dorsal spine equal bilaterally.

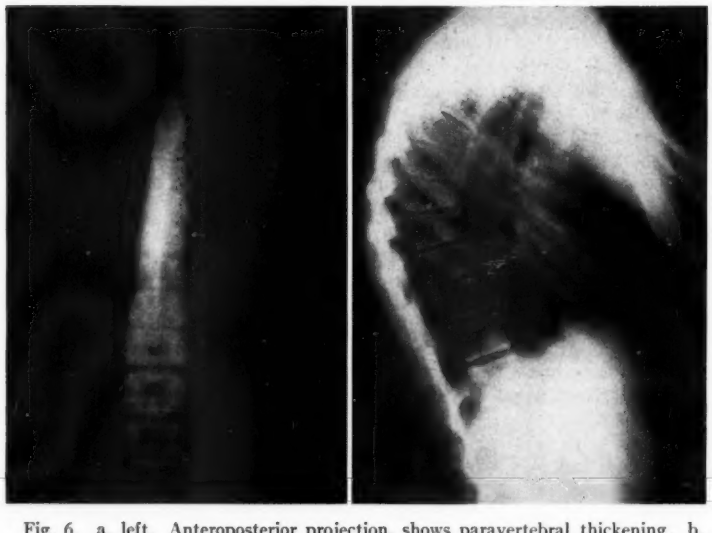


Fig. 6. a, left. Anteroposterior projection, shows paravertebral thickening. b, Lateral projection, shows increased dorsal curve, wedging of bodies, herniation of nuclear substance with reactive changes in bodies, and decreased intervertebral disc space.

The forward bend position accentuates the arcuate curve of the dorsal spine. Those individuals with tenderness bend slowly and with a splinting action of the erector spinae group. This protective mechanism is clearly seen in the attempt to gain the erect position from the forward bend attitude. *The erect position is gained by first straightening the dorsal spine on the flexed lumbar spine. Following this maneuver, the entire trunk is brought into extension.* This is a definite segmental movement as contrasted to the usual supple cooperative extension of all the segments of the normal spine, and in our experience a diagnostic sign from a clinical standpoint.

The patient with a rigid back on attempt at side bending, and torsion does so with the hips, the lumbar spine acting in a minimal capacity. Hyperextension is a protected movement. Less rigid backs will perform these maneuvers in an almost normal fashion except for the segmental movement on gaining the erect posture from forward bend.

The spasm of the erector spinae is more evident in the dorsal and dorsolumbar regions. The musculature is tight and not infrequently tender to pressure. The lumbodorsal fascia may be contracted thus contributing to the lordosis. Hyperextension of the knees and relaxed or pronated feet are common. The pronated foot is observed at a 45 degree angle or greater. Seldom do the feet plant themselves parallel, in assuming a posture.

Unilateral tightening of the hamstring muscles has been credited for scoliosis. We have observed scoliosis in a small percentage of these children (Fig. 4), but have, to date, seen only one case of tightened hamstrings, bilateral. The kyphoses observed with a scoliosis have not shown roentgen evidence of abnormalities that may be said to be the cause of the lateral curve. One may find, of course, other changes of a congenital nature in the vertebral bodies that may accompany the kyphosis and produce the scoliosis. The logical explanation is the interruption of growth laterally as well as ventrally. The scoliosis may be either to right or left and is not severe. The rotation is away from the convexity.

The typical picture, then, is that of a generally rounded back with limited mobility, relaxed abdomen, increase in lordosis, and hyperextension at the knees. So far in our experience we have not seen the severe rounded kyphos as depicted in foreign publications. Some of these approach the angular kyphosis. It is not logical to assume that the capacity of the spines of European children is less than our own children. However, the demands made upon the backs of the European child may well be greater during this child's growing period. The economic status of this country and that of Europe differ greatly. More physical labor may be demanded of the child in Europe than in our own States.

ROENTGEN FINDINGS

The generally accepted criteria necessary to make a diagnosis of juvenile kyphosis are (Fig. 6): (1) increased dorsal curve; (2) anterior wedging of the vertebral bodies in the dorsal region; (3) diminution of the intervertebral joint space; (4) serration of the anterior surfaces of the bodies; (5) nuclear herniations into vertebral bodies; (6) paravertebral thickening.

The increased dorsal curve as seen in the lateral projection is a generally rounded arc; the anterior vertical height of the vertebral body less than the posterior vertical height. This wedging plus the narrowing of the intervertebral spaces produce the exaggerated curve. These findings occur in the low dorsal spine, usually from the seventh dorsal downward. Changes higher up are, however, seen.

Wedging of the bodies is due to arrested growth anteriorly. In the lateral projections the superior or inferior surfaces of the bodies may exhibit an arc-shaped or semicircular area of rarefaction immediately beneath which is found a circular zone of increased density due to irritative bone production. The escape of nuclear substance into the spongiosa releases tension within the intervertebral disc thus allowing collapse and the resultant picture of decreased intervertebral space.

Saw-toothed serrations of the anterior borders of the vertebral bodies are said to be the result of pressure phenomena exerted on a softened vertebral body. These serrations appear at the metaphyseal areas superiorly and inferiorly. One hesitates to accept the explanation of softened bone structure as we believe the vertebral body not primarily involved in the pathological process.

The irregular punched out areas seen on the superior and inferior anterior surfaces, so called "saw cuts," are not a part of the roentgen picture in arriving at a diagnosis. On the contrary they are calcifying or ossifying areas of the "corona" about the vertebral body in different stages. This is a picture of normal development.

Paravertebral thickening in the anteroposterior projection is described by Brailsford. This thickening runs along the lateral borders of the spine in the area affected. The significance is not definitely understood.

In the late stages one may see secondary arthritic changes. The close approximation of the vertebral bodies resulting from the collapsed disc may allow bridging. Lipping of margins may develop.

TREATMENT

Treatment naturally seeks to bring an end to symptoms and arrest or correct the existing deformity. Fundamentally, one attempts to establish a balance between the capacity of spine and functional demand. This balance is established during actively supervised treatment, namely by support, rest, and limitation of activity.

One may arbitrarily divide the treatment into three stages: (1) the period between the time the diagnosis is made to cessation of ache, pain, or fatigue; (2) from the cessation of symptoms to return to work and activity or, normal range and exertion; (3) from this point of activity to cessation of the growth period. It may be well to state that, in some cases, one may not get a patient to normal range of activity in the second stage, and it is only when the growth is complete that the individual reaches a normal sphere of activity. In other words, there is no second period here.

It is our belief that one cannot expect to change the general contour of a wedged vertebra when once developed. However, one can expect better posture and stronger spinal musculature under treatment. The clinical complaints of ache and fatigue are alleviated by adequate rest and support.

On arrival at a diagnosis the patient is placed at rest. By rest is meant flat in bed, being up only for a short time as demanded by meals and bathroom privileges. No other time periods are allowed the first 30 days. The bed should have a hard or firm mattress. The inner spring mattress is not tolerated. Boards placed longitudinally beneath the mattress and on the springs suffice. If there is a fair degree or well developed kyphosis, the child is fitted to a plaster-of-Paris shell.

The shell is made with the patient on his abdomen. The body must be straight on the table and a pillow under the abdomen to obliterate the lumbar lordosis. Plaster bandage is laid across the back, carried to the midaxillary line laterally and extends from gluteal crease to base of the scapulae. After 5 or 6 layers, a re-enforcing strap iron is placed in the long axis over these layers, having been bent to the contour of the back. These are incorporated with 4 or 5 more layers. Canvas strap is also incorporated to cross the shoulders and circle the abdomen to facilitate holding the shell snugly to the body. It is well to remember that this shell must be molded carefully about the hips and held snugly here while setting. After the setting the upper portions beneath the axillae are shaved down so that there is free movement of arms and no pressure dorsally to crowd the shoulder girdles ventrally. The shell after this process is then filled in with plaster cream in the dorsal portion which exhibits the

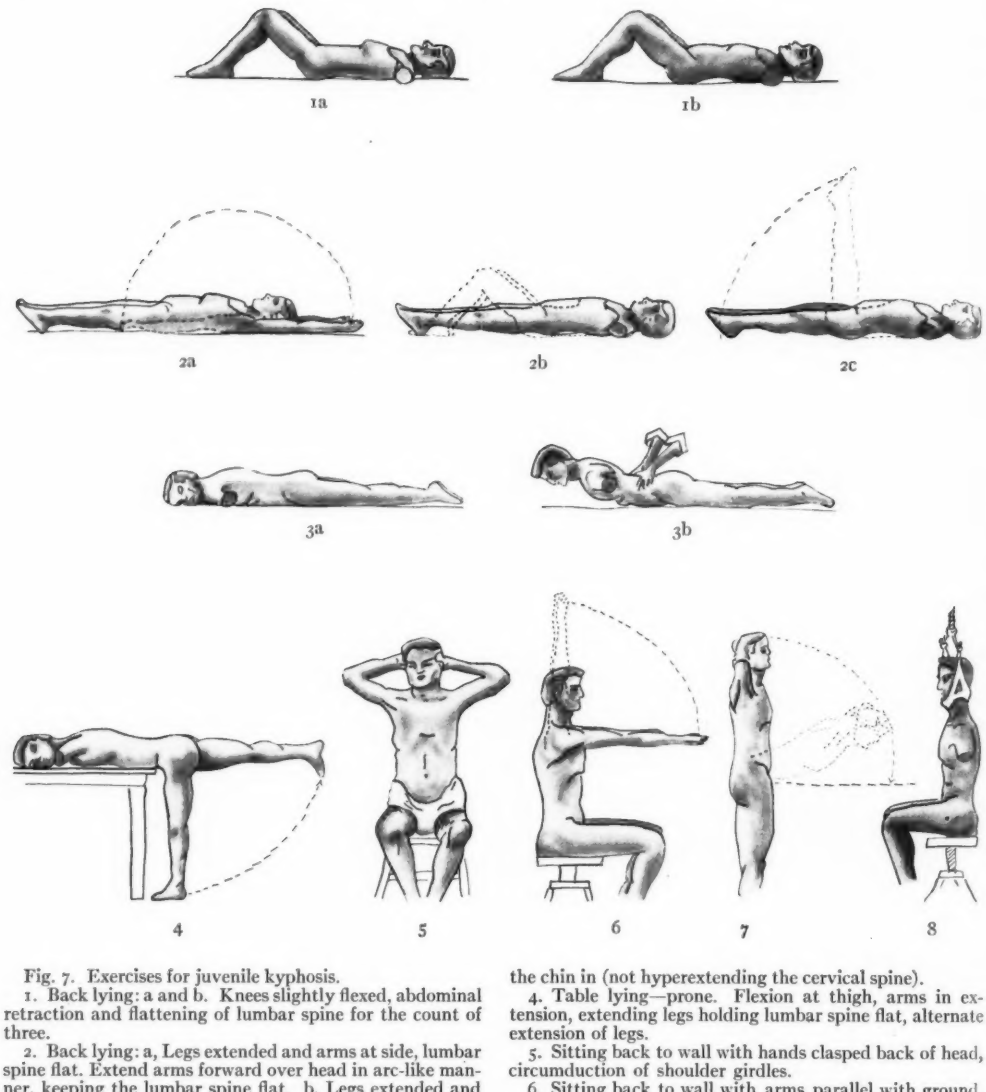


Fig. 7. Exercises for juvenile kyphosis.

1. Back lying: a and b. Knees slightly flexed, abdominal retraction and flattening of lumbar spine for the count of three.

2. Back lying: a, Legs extended and arms at side, lumbar spine flat. Extend arms forward over head in arc-like manner, keeping the lumbar spine flat. b, Legs extended and arms at side, lumbar spine flat. Bring legs into flexion keeping lumbar spine flat, relaxing down to extension maintaining the lumbar spine flat. c, Legs extended and arms at side with lumbar spine flat. Raise leg with knee in extension and foot at right angle to leg. Slowly descend to extension with lumbar spine *flat*.

Note: These exercises must be done on a flat hard surface.

3. Prone lying: a, Arms at side extension of dorsal spine from prone position. Attendant's hand at high lumbar spine so that only dorsal spine is exerting extension (preventing lordosis). The head must be held in extension with the chin in (not hyperextending the cervical spine).

4. Table lying—prone. Flexion at thigh, arms in extension, extending legs holding lumbar spine flat, alternate extension of legs.

5. Sitting back to wall with hands clasped back of head, circumduction of shoulder girdles.

6. Sitting back to wall with arms parallel with ground, overhead extension maintaining erect and extended lumbar spine.

7. Standing exercises: Arms clasped back of neck with lumbar spine flat, forward bending with *hips*, maintaining lumbar spine and dorsal spine in extension.

8. Sitting: Sayre head sling stretching.

Note: These exercises are to be given beginning approximately at five times and going up, keeping beneath the level of fatigue and discomfort. Patient gradually working into the table flexion, sitting, and standing exercises from initial back lying and prone lying exercises.

greater kyphotic point. It is well not to fill in completely to give a flat surface initially, gradual obliteration of the kyphotic impression can be accomplished over a period of 1 to 2 months without discomfort to the patient.

Some children will not tolerate this plaster mold over an hour a night in the early periods of treatment. Usually it is the patient with spasm. This condition is met by baking twice daily for 30 minutes followed by mild relaxing massage. When physiotherapy is available it is carried out in a regular schedule. Next best is teaching the parent the technique of massage and baking at home. We are convinced that the physiotherapeutic measures have much to do with the relief of symptoms, and in these cases exhibiting spasm, are just as important as rest.

The competent physiotherapist working daily with a patient will determine the gradual disappearance of spasm in the erector spinae group and in conjunction with the attendant, arbitrarily determines the gradual increase in activity. If after a month the back is free of ache and is more or less loosened up, the child is allowed periods of supervised activity. These may be 1 or 2 hours in the mid-morning and the same period in mid-afternoon. Between times the patient continues to remain at rest in the shell.

At this period are begun exercises in addition to the bakes and massage. Initially, they are back lying and prone maneuvers to be described. They are supervised by the physiotherapist who can gauge the time and vigor of the exercises, gradually adding to the routine.

As the child develops tolerance and strength, standing exercises are brought in, and, when the patient fully understands the routine, he is allowed more time and activity.

In those patients with a well developed kyphosis wherein the posture does not correct, a spinal brace[1] is applied. It is constructed high in front with pressure points just below the clavicles and low in back. These patients earlier in the treatment, after a month of rest, may be placed in a plaster-of-Paris body cast molded high in front and low in back. We have made it a practice of keeping this cast on a child from 3 to 6 months, changing plasters each 2 months as necessary. Not infrequently a semi-permanent celluloid jacket is used.

The ambulatory case, when an out-patient, continues his exercises and wears the shell nights. If in a brace, this same routine continues. In cases in which carriage and posture are now the only problem, the massages and bakes are discontinued. On the patient is placed the responsibility of exercises and the wearing of the shell at night.

How long restricted activity continues and to what degree, depends upon posture and the clinical picture of the back. These factors are determined only by repeated clinical examination. In our experience repeated x-ray examination has been of no practical value over short periods of time (under 6 months). If after 6 to 18 months the posture remains satisfactory and there are no complaints, the plaster or spinal brace is removed half days. It is during this period that a discrepancy may arise between the capacity and function; the continued absence of symptoms, laxity on the part of the patient and parent may allow too much activity and symptoms return. The conscientious patient progresses without pain and the support is removed completely.

A year to 18 months in a brace is not excessive, and in children of 12 to 15 years 3 or 4 years is not unusual. As the patient grows and develops a greater muscular capacity, his activity increases and gradually he enters the sphere of normal exertion. Stage three continues up to cessation of the growth period, and the properly supervised individual will keep his carriage and posture through this period.

It is interesting to note that our foreign contemporaries have an advantage in handling children. The regimentation of the child in large clinics is an accepted fact and classes are held daily with obligatory attendance. The classes are uniformly carried out with specified exercises and over long periods of time. We are of the opinion that if these adolescents are not protected from themselves until they fully appreciate their condition or until the full growth is attained, they are sowing seeds of chronic indefinite low grade backache of later years.

CONCLUSIONS

1. Juvenile kyphosis is a clinical entity of not uncommon occurrence. It is seen most frequently between the ages of 10 and 14 years, females predominating.

2. The true etiology is not definitely understood.

3. Roentgenograms reveal a characteristic picture.

4. Juvenile kyphosis is a self-limited disease. Treatment aims to alleviate symptoms and arrest the deformity through rest, physiotherapy, and temporary spinal support.

5. Juvenile kyphosis, if not properly treated may lead to chronic backache and to permanent deformity.

[1] Described in Chapter 3, Jordan's Orthopaedic Appliances (13).

BIBLIOGRAPHY

1. Boorstein. Osteochondritis of the spine. J. Bone & Joint Surg., 1927, 9: 629–635.
2. Brailsford, James F. Radiology of Bones and Joints, 295, 357. Baltimore: William Wood & Co., 1934.
3. Buchman, Joseph. Résumé of osteochondritides. Surg., Gynec. & Obst., 1929, 49: 447.
4. Bucy, P. C. and Cloward, R. B. Spinal extradural cyst and kyphosis dorsalis juvenilis. Am. J. Roentgenol., 1937, 38: 681–706.
5. Burns, B. H., and Ellis, V. H. Recent Advances in Orthopaedic Surgery, 182–188. Philadelphia: P. Blakiston's Son & Co., Inc., 1937.
6. Calve and Galland. The intervertebral nucleus pulposus; its anatomy, its physiology, its pathology. J. Bone & Joint Surg., 1930, 12: 555.
7. Dueno, F. P. Juvenile dorsal kyphosis. Arch. de med., cirug. y especial. 1935, 38: 256–271.
8. Frejka, B. Infantile kyphosis. Rev. d'orthop., 1938, 25: 110–124.
9. Idem. Adolescent kyphosis. J. Bone & Joint Surg., 1932, 14: 545–554.
10. Haas, S. L. Experimental production of scoliosis. J. Bone & Joint Surg., 1939, 21: 963–968.
11. Idem. Growth in length of vertebrae. Arch. Surg. 1939, 38: 245–249.
12. Harbin, M., and Zollinger, R. Osteochondritis of the growth centers. Surg., Gynec. & Obst., 1930 51: 145.
13. Jordan, H. H. Orthopaedic Appliances. New York: Oxford University Press, 1939.
14. Meyer, Marcel. La cyphose douloureuse des adolescents: son substratum anatomique. Rev. franç. de pediat., 1932, 8: 285–311.
15. Schanz, A. Schule und Skoliose. Jahrb. f. Kinderh., 1911, n.F., 73: 1–26.
16. Scheurmann, H. Kyphosis dorsalis juvenilis. Ztschr. f. orthop. Chir., 1921, 41: 305.
17. Idem. Roentgenologic studies of the origin and development of juvenile kyphosis together with some investigations concerning vertebral epiphyses in man and animals. Acta orthop. Scand. 1934, 5: 161–216.
18. Schmorl, George. Pathogenesis of juvenile kyphosis. Fortschr. a. d. Geb. d. Roentgenstrahlen, 1930, 41: 359–383.
19. Schuldbach, Johannes. The development of juvenile kyphosis. Zentralbl. f. Chir., 1937, 36: 2086–2104.

THE RESULTS OF SPLENECTOMY IN GAUCHER'S DISEASE

VICTOR W. LOGAN, M.D., New York, New York

IN 1882 Gaucher described the splenomegaly which bears his name. He considered it a primary tumor of the spleen, but later investigators, notably Pick (22), Mandelbaum, and Epstein have shown that it is due to a disturbance of lipoid metabolism, resulting in the deposit of kerasin in the cells of the reticuloendothelial system.

The clinical features of the disease are a progressive splenomegaly, a tendency to hemorrhage, brownish yellow discoloration of the skin, and wedge-shaped pingueculae. As the Gaucher cells develop in organs other than the spleen, they give rise to secondary clinical types. An osseous form of Gaucher's disease has been described by Pick (23). Destruction of bone with fracture or deformity occurs in about half of all cases. Neurological signs may predominate, especially in infants (1). Lesions of the lung (19) and kidney (14) have been described. The liver enlarges more slowly than the spleen, and a late cirrhosis may occur. Lymph nodes are occasionally enlarged.

The blood picture is not striking. There is a mild anemia with leucopenia. The differential count is normal. The thrombocytes are often reduced, but the bleeding and clotting time are normal. The fragility test is normal.

Diagnosis can be made from examination of the bone marrow by sternal puncture (33), which has displaced the dangers of splenic needling. Biopsy of an enlarged lymph node revealed the diagnosis in the cases reported by Hoffman and Makler and Donovan. The Gaucher cell is a large endothelial cell with grayish white cytoplasm containing fibrillae. The nucleus is small and eccentric. The cell contains the lipoid kerasin, a cerebroside.

The disease is familial, congenital, and possibly hereditary. Anderson has suggested that it is transmitted by unaffected males. (My own case lends some support to this idea.) Although it appears to have a predilection for the Jewish race, it occurs in members of all races, including negroes (13, 29) and orientals (31). Contrary to former belief, the sex incidence is about equally divided between males and females. Atkinson analyzed 103 cases (children) of whom 53 were females and 50 males.

Gaucher's disease usually becomes established early in life, but the progress of the illness is so chronic in some cases that it escapes notice until long after maturity. Siegmund's case, quoted by Hoffman and Makler is the youngest patient on record, being 1 week old. Wechsler and Gustafson recently reported a case in a woman 71 years of age. Horsley and his associates found in a study of 71 cases, that over half of them were recognized before the age of 8 years.

Death usually results from intercurrent infection, often pneumonia. Melamed and Chester's patient, and Ullrich's also, died of the osseous form. Rowland and Aballi and Kato have called attention to an acute, fatal, infantile form with neurological symptoms.

Gaucher's disease is closely allied to the other disorders of lipoid metabolism. These are Niemann-Pick disease and Hand-Schuller-Christian disease. Tay-Sachs disease (congenital familial amaurotic idiocy) is now considered to be a cerebral form of Niemann-Pick disease. These "xanthomatoses" have been amply discussed by Pick (22).

There is no specific treatment for the disease. Potter and McRae felt that liver extract helped one of their patients, but there has been little subsequent enthusiasm for this suggestion. X-ray radiation over the spleen had no retarding influence on the growth of the organ in either Pack's case or mine. In both cases it produced anemia, and therefore it seems to me to be a harmful treatment. Splenectomy, which was first performed for Gaucher's disease in 1895 (24), remains the most hopeful palliative measure. The principal objection to the operation is its high mortality. There is a conviction, possibly based on the first 10 recorded splenectomies for Gaucher's disease (11) that the operative risk is 20 per cent, since 2 of the 10 patients succumbed. Atkinson states that 7 of the 47 children, who had had splenectomy for Gaucher's disease, died after operation. This suggests a mortality rate of about 15 per cent in children. Whipple reported but 10 deaths in 106 splenectomies performed for various reasons in his Spleen Clinic at the Presbyterian Hospital. Since the Gaucher spleen, while enormously large, is one of the easiest spleens to remove, owing to the fact that it is rarely adherent, the current mortality rate must be much less than 20 per cent.

The immediate effect of splenectomy in exsanguinated children is often miraculous. Both

Myers' (19) and Ullrich's infants were essentially moribund prior to operation. Several authors, including Mueller have felt that splenectomy hastened the rate of bone involvement. However, de Lange who had followed two sisters for 9 years, observed that the skeletal changes were less marked in the splenectomized girl, although both children had lesions of the hip and tibia.

Indications for splenectomy are hemorrhage (especially when the platelet count falls below 100,000) and the discomfort of a large abdominal tumor. In Pool's case (25) the compelling reason was a desire to bear children, as the first pregnancy had terminated in a miscarriage. Hunter and Evans reported that their patient had 3 miscarriages, attributed to the enlarging spleen.

Late reports on splenectomized cases are unfortunately rare. For this reason I am reporting a new case 7 years after operation, and shall present notes on the present status of several well known cases previously described in American literature.

REPORT OF CASES

A. S., a young unmarried woman, 28 years of age, was referred to us in January, 1932, by Dr. Bernard Samuels because a small incision of the lower eyelid had bled for 4 days. Two years previously, she had bled overmuch after the extraction of a tooth. Nose bleeds were rare, but bruising was common. She had lost 7 pounds from dieting to reduce the size of her abdomen. No pain or dragging had been felt. She was employed in a useful capacity in the office of a hospital planning expert.

The family history was interesting. Her father was half Jewish, but there was no other Jewish ancestry. One of her brothers had a large spleen. He was 2 years younger than his sister and had known for 16 years (from the age of 10) that his spleen was enlarged. As he lived in a malarial region of Louisiana, no attention had been paid to it yet he had never had chills and fever. During the 3 years he was under observation in New York the spleen did not increase in size. His blood count in May, 1932, was normal.

Physical examination of the patient showed a tall, pale young woman, with a small healing incision of the lower right eyelid, oozing blood. The heart and lungs were normal. Traube's space was flat on percussion. The abdomen was full, especially on the left. A hard, smooth mass filled the entire left half of the abdomen, with a notch at the umbilical level. The mass extended deeply into the left iliac fossa. The liver edge was not felt. There were several large bruised areas on the shins, and one over the thigh. Superficial lymph nodes were not enlarged. There was no pigmentation. Pingueculae were absent.

The patient was quite anemic and had a leucopenia, as shown in the accompanying blood tabulation. The thrombocyte count was 250,000. The blood loss was quickly made up after control of the bleeding by suture. The spleen continued to grow, but there were no symptoms except fatigue. The diagnosis seemed reasonably clear for Gaucher's disease, but it was suggested that x-ray therapy be tried. This merely resulted in restoring anemia, without controlling the continued growth of the spleen. By the end of March the organ was occupying much of the right iliac fossa, having crossed the midline like a boot. Operation was recommended because of the great size of the spleen.

The patient elected to go to her home in Shreveport, where, on June 5, 1932, Dr. E. L. Sanderson of that city took out the spleen and sent me his operative report: "We removed the spleen, which weighed 9 pounds after removal. Of course it was much larger, until we tied the artery and applied gentle pressure before tying the veins. There were no adhesions and the operation was comparatively easy. She has had an uneventful recovery. Our pathologist makes a positive diagnosis of Gaucher's disease." This was also the opinion of Dr. Ralph G. Stillman of New York Hospital, to whom I submitted a section of the spleen, sent by Dr. Sanderson.

Following her convalescence, the young woman came back to New York, where she resumed her work. Last year (1939) she returned to her home to look after her mother, who was ill. There has been no clinical evidence of bone involvement, although no recent films have been made. Studies in 1933, about a year after operation, showed minimal thinning of the cortex of the femur shafts. The blood count shows a slight reduction in the red cells and a persistent leucocytosis, with normal differential count. On one occasion 1 nucleated red cell was seen per 100 white blood cells. Pigmentation and pingueculae have not developed. The patient says that she feels fine.

Pool's case. In 1921 Pool (25) reported the case of a young married Jewish woman, 25 years of age, who had in the past year begun to lose weight and strength. She had been explored by another surgeon, who presumed that the cause of a miscarriage was an ovarian cyst. Although the mass was identified as a spleen, it was not removed. Five months later she came under Dr. Pool's observation. He found an enormous spleen, extending to the anterior superior spine on the right and almost into the pelvis.

Splenectomy was done on January 25, 1921, because the patient desired to have children. Pre-operative studies of the blood showed a mild secondary anemia, without leucopenia, while the platelet count was normal. Pathological studies of the spleen showed typical Gaucher's disease. The case is fully documented in the monograph *Surgery of the Spleen* by Pool and Stillman (28).

In 1928, 7 years later, Pool (26) again reported the case: "Her health has been good with one exception. Four years ago her left hip became painful. It was put in plaster in another hospital for 6 weeks and the joint is now immobile and painless. She has a decided limp . . . examination of the skull and other bones shows no evidence of disease except in the left hip joint, where there is a definite destructive process involving the head of the femur. The head is mottled . . . there is definite bone absorption and irregular calcification . . . the greater trochanter shows a decalcifying process and the medullary substance in the shaft shows mottling for about two-thirds of the shaft. These changes were interpreted as . . . the result of Gaucher's disease."

In 1930 Pool and Hipsley (27) reported that the bone changes in the hip had not progressed and that no new lesions had occurred. At this time the patient had 2 living children and was expecting a third.

Dr. Pool has kindly allowed me to make use of his recent notes on this woman, who is now 44 years old. Nineteen years have elapsed since the splenectomy. In the past year she has had some pain in her left shoulder. X-ray of this region shows no bone destruction, although one observer thought there was some cortical thinning. The hip has shown no further change. A sternal bone marrow puncture revealed no Gaucher cells, which seems remarkable. The blood picture is given in the accompanying table. There is no pigmentation of the skin and the liver is not enlarged. Pingueculae have not appeared. The patient looks well.

BLOOD COUNTS, CASE A. S.

Date	Hb. %	R.B.C.	W.B.C.	Poly. N. %	Lymph. %	Mono. %	Eosin. %	Baso. %	Nucl. R.B.C per 100 W.B.C.
1-13-1932	60	2,940,000	2,800	54	42	3		1	
2-9-1932	75	4,400,000	3,400	65	34	1			
X-ray therapy									
3-18-1932	60	3,850,000	1,200	75	22	3			
Splenectomy, June 5, 1932									
7-5-1933	96	4,295,000	14,150	49	42	6	3		
10-25-1933	75	3,536,000	12,500						
1-25-1938	82	4,040,000	22,000	56	37	5	1	1	
10-31-1938	106	4,100,000	24,000	57	27	11	3	2	1
10-17-1939	105	4,560,000	18,800	64	27	6	2	1	

Hb. %, hemoglobin, per cent; R.B.C., red blood cells; W.B.C., white blood cells; Poly. N., polymorphonuclear neutrophiles; Lymph., lymphocytes; Mono., mononuclears; Eosin., eosinophiles; Baso., basophiles; Nucl. R.B.C. per 100 W.B.C., nucleated red blood cell per 100 white blood cells.

BLOOD COUNTS, POOL'S CASE

Date	Hb. %	R.B.C.	W.B.C.	Poly. N. %	Lymph. %	Mono. %	Eosin. %	Baso. %
1-24-1921	82	4,200,000	9,800	60	36	3	1	
Splenectomy, January 25, 1921								
1-7-1929	68	3,860,000	20,100	72	24	3	1	
4-21-1930	80	4,100,000	13,500	43	51		4	2
5-6-1931	67	3,340,000	12,700	73	24	3		
5-3-1939	90	4,000,000	16,000	58	29	8	4	1

BLOOD COUNTS, ERDMANN AND MOORHEAD'S CASE

Date	Hb. %	R.B.C.	W.B.C.	Poly. N. %	Lymph. %	Mono. %	Eosin. %	Baso. %	Myelocytes
2-28-1912	85	6,200,000	7,000	40	49	9	1	1	
Splenectomy, June 6, 1912									
4-22-1913	75	5,300,000	16,000	43	47	8	1	1	
4-17-1924	75	4,480,000	12,000	48	42	4	3	1	
1926			8,000						
1930	65	3,650,000	11,750	54	42	3	1		
1- -1932	77	5,600,000	19,200	43	40	16	1		
4-10-1935	72	4,350,000	19,600	55	37	8			
2-7-1936	80	4,350,000	19,125	62	27	7	3	1	
5-14-1937	65	4,250,000	27,200	54	8	34		3	1
6-22-1938	65	3,110,000	20,000	50	44	5	1		
7-31-1939	60	2,900,000	12,800	49	48	1	2		
8-29-1937	74	4,150,000	14,000	44	51	1	3	1	
1-3-1940	85	4,120,000	28,000	50	38	7	3	2	
2-27-1940	83	4,400,000	12,360	70	18	8	1	3	

Dr. Paul Reznikoff, who did the last count, made the following comment: "Anisocytosis 1 plus; poikilocytosis 1 plus; toxic granulation 1 plus. Bleeding time 1½ minutes; tourniquet test slightly positive, flicking test moderately positive; clotting time 38 minutes (normal 10–12 minutes); clot retraction fairly good; clot fragility, quite fragile; hematocrit 36.5 per cent; volume index 0/98; prothrombin 55 per cent normal; fibrinogen 0.2 (normal); reticulocytes 2.3 per cent, platelets 300,000; 1 nucleated red blood count in smear."

Erdmann and Moorhead's case. In 1914 Erdmann and Moorhead reported the case of a girl, 3¼ years old, upon whom they had performed a splenectomy for Gaucher's disease on June 6, 1912. This was the tenth splenectomy for Gaucher's disease reported in the world literature. This child was the fourth in the family. Her eldest brother had developed, in the second year of his life, a large liver and spleen, with anemia and leucopenia. At the age of 6 he died of a fulminating pneumonia. Although no autopsy was done, he presumably had Gaucher's disease.

At the time of the girl's operation, the liver extended 2 inches below the ribs, and the spleen reached below the umbilicus and beyond the median line. Splenectomy was performed because of progressive loss of strength. Diagnosis was confirmed by studies of the spleen. The authors' final notes were made on October 6, 1913, 16 months after the operation, when the child was reported well and strong.

She is now 31 years of age. The only dramatic episodes since the operation have been an appendectomy in 1929, without complications, and a severe fall from a horse in 1936. This resulted in a compression fracture of the body of the second lumbar vertebra, without serious sequelae. Films of the spine at this time failed to show evidence of Gaucher cell infiltration.

In 1931 the liver extended to the umbilical level in the mid-clavicle line. The veins on the anterior chest wall were prominent. Mitral and aortic systolic murmurs were noted. In 1939 there was a transient numbness of the right hand.

While this patient cannot be considered to be in perfect health, she has not suffered from gross bone destruction nor has she developed a severe or persistent anemia. The enormous liver may portend an eventual cirrhosis syndrome. I have been unable to find any other case in the literature which has been followed as long as this one, 28 years, since splenectomy. It abundantly refutes Mueller's conclusions that the "outcome of all patients operated upon at a young age is death either shortly after the operation or a few years later" (18).

Pack and Silverstone's case. In 1938 Pack and Silverstone reported a case of Gaucher's disease occurring in a 25 year old single Jewish woman, who came to the clinic of the Memorial Hospital in 1932. She gave a history of progressive enlargement of the spleen and severe epistaxes for 3 years, and was found to have a large spleen and liver, a mild anemia with leucopenia, and a symptomless infiltration of the upper lobe of the left lung. After an absence of 3 years, she returned in January, 1935, having developed pigmentation of the legs, a slight productive cough, and further enlargement of the spleen and liver. She had had one small hemoptysis. The blood picture revealed a marked anemia, with a platelet count of but 67,000. Because of the purpuric manifestations, which were obviously due to the thrombocytopenia, splenectomy was performed on May 4, 1935. The spleen weighed 3500 grams.

Improvement following the operation was striking. She gained 21 pounds in 4 months, the liver returned to normal size, and the blood platelets rose to 320,000 with corresponding increase in all the blood cells. In spite of the clinical improvement, films of the chest showed increased infiltration. Pack's comment on the lung lesion was "the infiltrative process in the left upper lobe of our own case was interpreted as probable tuberculosis, but in the absence of confirmatory evidence for tuberculosis Gaucher cell infiltration may reasonably be considered."

Eleven months after splenectomy pain occurred in the right knee. Films at this time revealed osteoporetic changes in both femora and tibiae, with no changes in other bones. Her general health was good.

Dr. Pack has kindly furnished me with recent notes on this patient. Late in 1938 tubercle bacilli were identified in the sputum and since then the patient has been treated by her family physician. He reports continued small hemoptyses in spite of repeated artificial pneumothorax treatments. Gaucher cells have not been reported in the sputum.

There has been increasing involvement of the skeletal system, especially in the upper portion of the right femur, which showed a pathological fracture in December, 1939. At the present time, April 8, 1940, the patient is still on crutches. Films in January, 1930, showed osteoclastic areas in the shaft of the left humerus and destruction of the right ilium, sacrum, and pubis. The patient is fairly anemic.

The rapid rate of involvement of the skeletal system in this patient suggests a poor prognosis. However, it is interesting that the right tibia, the first bone involved, has shown remarkable healing power. This phenomenon has been seen in Pool's case and was also commented on by de Lange.

In spite of the finding of tubercle bacilli in the sputum since the publication of this case, one wonders whether the original infiltration, so long silent, was not due to Gaucher cell infiltration, with secondary tubercular infection. Myers' de-

BLOOD COUNTS, PACK AND SILVERSTONE'S CASE

Date	Hb. %	R.B.C.	W.B.C.	Poly. N. %	Lymph. %	Mono. %	Eosin. %	Baso. %
1- -1935	60	2,848,000	3,200	46	45	5	3	1
Splenectomy, May 4, 1935								
11- -1936	80	4,192,000	15,700	50	41	7	2	
12-26-1939	70	3,576,000	10,300	64	35		1	
2-26-1940	60	3,220,000	9,900	60	20	18	2	

scription of the lungs in his patient showed many points of resemblance to the lung lesion of this case, but without the finding of tuberculosis at autopsy. Hoffman and Makler state that 8 of the 89 cases reviewed by them (including Gaucher's case) succumbed to tuberculosis. Perhaps more critical study of the lungs of these patients would have revealed Gaucher cell infiltration.

Cushing and Stout's case. In 1929 Cushing and Stout reported 2 cases of Gaucher's disease. Dr. Stout tells me that he has no further information about the first case.

The second case was that of an American woman of 33 years of age, who had suffered from childhood from severe epistaxes. At the age of 29, *3½ years before splenectomy,* she had developed stiffening, pain, and shortening of the right hip. She had all the stigmas of Gaucher's disease. On August 26, 1924, Dr. Whipple removed her spleen. which weighed 1017.5 grams. In 2 months she had gained 17¼ pounds, pigmentation lessened, and the liver was no longer palpable. In December, 1924, the head and neck of the femur were resected and sequestrums removed. Gaucher cells were found in great numbers in these fragments. The authors' last report stated that in April of the following year the lower part of the right femur had become involved.

This patient is now 49 years old, and 15 years have elapsed since her splenectomy. She is being followed in Dr. Whipple's Spleen Clinic at the Presbyterian Hospital. Data regarding this patient will doubtless appear in future publications from that source. She is moderately anemic (see Table II).

TABLE I.—RESULTS OF SPLENECTOMY 5 OR MORE YEARS AFTER OPERATION

Author	Years after operation	Remarks
Erdmann and Moorhead	31	No bone lesions. Liver large
Pool	19	Left hip involved 3 years after operation. Now quiescent
Cushing and Stout	15	Right hip involved 3½ years before operation. Now under supervision at spleen clinic, Presbyterian Hospital
Hunter and Evans	13	No bone involvement Occasional hemoptysis Liver enlarged
de Castro Freire	11	No complications
de Lange	8	Liver enlarged Left hip-joint, left tibia involved after operation with subsequent "healing"
Logan	7	No complications
Melamed and Chester	7	Died from extensive osseous type Involvement of bone antedated operation by 7 years
Muller (Ullrich's case)	6	Extensive osseous invasion soon after operation. Died
Myers	5½	Both femurs involved soon after operation. Died of pulmonary Gaucher cell invasion and progressive osseous destruction
Pack and Silverstone	5	Right knee involved soon after operation with later fracture o right femur, and involvement of left shoulder. Pulmonary tuberculosis

OTHER LATE REPORTS ON SPLENECTOMIZED CASES

De Lange, already referred to, followed two sisters for 9 years, one of whom had been operated on. She found that the liver increased in size at first after splenectomy, but in later years ceased to enlarge. Pigmentation appeared in both girls at the same ages, but later disappeared in the splenectomized girl. This observation has been made by others. Both children had destructive lesions of the left hip joint.

Mueller gave the final report of Ullrich's case. This child of 3, in 1930, was almost *in extremis* from uncontrollable nasal hemorrhage, and made a remarkable postoperative recovery, only to succumb to an osseous form of the disease, with terminal meningeal symptoms at the age of 9. The finding of an accessory spleen the size of an apple, at autopsy, was one of the features of this case.

Myers (19) in 1937 reported the autopsy findings on a child 8 years old, who had had a splenectomy in September, 1931 (20). Just prior to operation the erythrocyte count was below 1,000,000, because of three severe nose bleeds. Contrary to expectations, the operation proved life saving. The lower end of the right femur was incised for a supposed osteomyelitis in April, 1932, Gaucher cells being found in the exudate. The dorsal vertebral bodies and the lower end of the left femur became involved during the next 2 years. In August, 1935, the lung became infiltrated and death came January, 1937, from a terminal bronchopneumonia. Gaucher cells were found in the enlarged mediastinal and hilum glands, while the air spaces of the lung were compressed by Gaucher cells developing in the small subserous and interlobular lymph nodes. There was no evidence of tuberculosis.

De Castro Freire in 1935 made a second report of the case which he had published in 1926. This concerned a girl of 8 years of age, the first case of Gaucher's disease to be reported from Portugal. Eleven years after her splenectomy, she was planning to marry at the age of 19. The liver had not enlarged and the hemorrhagic diathesis, which had been responsible for the decision to remove the spleen, had not recurred. There had been no apparent bone involvement.

Hunter and Evans have reported one of the oldest cases on record. This woman of 60 years of age became pigmented at the age of 8 and had nose bleeds from the age of 10 onward. When she was 29 the spleen was found to be enlarged. She

TABLE II.—LATE BLOOD COUNTS OF PATIENTS WITH GAUCHER'S DISEASE AFTER SPLENECTOMY[1]

Author	Hb. per cent	R.B.C.	W.B.C.	Poly. per cent	Nuc. R.B.C.	Platelets	Years after operation
Erdmann and Moorhead	83	4,400,000	12,360	70			31
Pool	90	4,000,000	16,000	58	1[2]	300,000	18
Cushing and Stout[3]	70	3,800,000	12,300	54	4/100	245,000	15
Hunter and Evans	67	3,900,000	8,480	65	1/200	120,000	12
de Castro Freire	66	3,440,000	13,400	49		66,000 (Spietz)	11
Logan	105	4,560,000	18,800	64	1/100		7
Melamed and Chester	48	2,900,000	6,000	40	280/100	90,000	6½[5]
Mueller	18	600,000	18,400	42	2/100	75,000	5½[4]
Myers	87	5,200,000	73,600	65			4
Pack and Silverstone	60	3,220,000	9,900	60			5

[1]The full differential leucocyte count is omitted because it shows no essential variation from the normal.
[2]Number in entire smear.
[3]Figures from spleen clinic, Presbyterian Hospital.
[4]Moribund.
[5]4 months before death.

had 2 living children and had had 3 miscarriages. Before her spleen was removed she had begun to have hemoptyses. After the operation, performed in her forty-seventh year, the abdominal pain, which was the reason for the splenectomy, disappeared. Pigmentation decreased. At the time of Hunter and Evans' report, 13 years after the operation, she tired easily, suffered from headaches, had developed pingueculae, and again suffered from occasional hemoptyses. Signs in the lung were negative. The liver edge was 2 inches below the costal border.

Melamed and Chester in 1938 gave the final report of a 26 year old male, who had suffered from an osseous type of Gaucher's disease from the age of 13 years. When he was 20 years old the spleen was removed. He had purpuric manifestations without thrombocytopenia before the operation and was largely relieved of these for some years. In the last years of his life the bone destruction was so marked that he was bedridden. Invasion of the bone marrow finally produced a malignant anemia, which was heralded by the appearance of increasing numbers of nucleated red cells (Table II).

ANALYSIS OF STUDY

In reviewing these cases, one is struck by the uniform improvement in the clinical picture immediately following splenectomy. Hemorrhage is controlled, the patient gains weight, the liver decreases in size, and pigmentation often lessens or disappears. The hemorrhagic diathesis is not always cured by splenectomy. Carling and his associates found that their patient continued to have hemoglobinuria after splenectomy. Hunter and Evans reported recurrence of hemoptysis after splenectomy, as noted, and Pack's patient has had similar experiences. Ullrich's patient is reported by Mueller to have had recurrent ecchymoses 2 years after operation. In most cases, however, hemorrhage does not recur and the thrombocytes maintain a normal level. The chief change in the blood picture after splenectomy is the replacement of a leucopenia with permanent leucocytosis. This is true of most of the cases reviewed in this paper. The differential count is essentially normal both before and after splenectomy. Nucleated red cells appear from time to time, but their numbers are not great until the bone marrow is almost completely replaced by Gaucher's cells in the malignant osseous type (see Melamed and Chester's case). The degree of leucocytosis appears to have no relation to the amount of bone destruction. It is probably a nonspecific reaction to splenectomy. Connors reported a leucocyte count of 13,000 in 1 of his patients 17 years after a splenectomy done for traumatic rupture of the spleen.

It has been alleged that splenectomy precipitates or hastens involvement of the bones in Gaucher's disease. This will be difficult to prove until someone has the opportunity to remove the spleen in one of a pair of identical Gaucher twins. De Lange felt that there was retardation of the skeletal involvement in the splenectomized girl as compared to the sister. Of the patients reviewed in this paper 2 had bone changes before splenectomy, 4 developed bone lesions after splenectomy, while 4 others had no evidence of skeletal

involvement in the 7, 11, 13, and 28 year periods following their respective splenectomies. As splenectomy is only done at a time when Gaucher cell infiltration is in a rampant phase, it seems unreasonable to attribute postoperative bone involvement to the mere removal of the spleen.

As a general rule, the earlier in life that the disease gives rise to symptoms, the worse the prognosis, and therefore the earlier the splenectomy, the worse the outlook. Yet Erdmann and Moorhead's case and de Castro Freire's show that one may not be arbitrary in withholding the benefits of splenectomy from young children. In neither of these patients has purpura recurred, nor have bone complications arisen.

As to the ultimate value of splenectomy in Gaucher's disease, the long histories of these patients is encouraging. The bone lesions in the older patients have not progressed to total skeletal involvement except in the fatal case described by Melamed and Chester, while in certain instances there has been evidence of arrest and repair. They are in fair general health and carry on as normal individuals. One of them has raised a family. Their present ages are 33, 36, 44, 48, and 1 was aged 60 in 1929 (Hunter and Evans' case).

Of the 5 children, 2 died before the age of 10 years. The others have arrived at the ages of 12, 19, and 31 years. Of the splenectomized patients who have died, 2 died of the malignant osseous form and 1 of the pulmonary form. None died as a result of intercurrent infection. Although this series of cases, followed for more than 5 years, is small, it is of interest to note that there has been freedom from acute intercurrent infection in the entire group. If splenectomy increases the resistance of the Gaucher patient to acute infections, which is reputed to be the chief cause of death in this group of individuals, the operation would be justified on this ground alone.

SUMMARY

1. A short review of Gaucher's disease is given, with the report of a case 7 years after splenectomy.

2. Late reports are made of several cases previously described in the literature, ranging from 5 to 28 years after splenectomy.

3. Similar cases from the world literature are reviewed.

4. The mortality rate for splenectomy in Gaucher's disease is nearer 15 than 20 per cent. Those patients who survive the operation show striking immediate clinical improvement, which is usually maintained, except in very young children.

5. The theory that splenectomy hastens the involvement of bone in Gaucher's disease is questioned.

6. It is suggested that splenectomy increases the resistance of the Gaucher patient to infection.

I wish to express my thanks to Dr. Eugene H. Pool, Dr. John J. Moorhead, Dr. George T. Pack, Dr. Arthur Purdy Stout, and Dr. Allen O. Whipple for their generosity in allowing me to use data on their cases from their private files.

BIBLIOGRAPHY

1. Aballi, A. J., and Kato, J. Gaucher's disease in early infancy; a review of literature and report of a case with neurological symptoms. J. Pediat., 1938, 13: 364–380.
2. Anderson, J. P. Hereditary Gaucher's disease. J. Am. M. Ass., 1933, 101: 979–981.
3. Atkinson, F. R. B. Gaucher's disease in children. Brit. J. Child. Dis., 1938, 35: 1–22.
4. Carling, E. R., Carlill, H., and Pulvertaft, R. J. Splenectomy in Gaucher's disease with hemoglobinuria. Proc. Roy. Soc. Med., 1932, 26: 361.
5. Connors, J. F. Splenectomy for trauma. Tr. Am. Surg. Ass., 1928, 46: 68–83.
6. Cushing, E. H., and Stout, A. P. Gaucher's disease; with report of a case showing bone disintegration and joint involvement. Arch. Surg., 1926, 12: 539–560.
7. de Castro Freire, L. De la splénectomie dans la maladie de Gaucher. Arch. de méd. d. enf., 1935, 38: 163–166.
8. de Lange, C. Ueber Zeitfolge des Entstehens und ueber Heilungstendenz der Skelettveraenderung beim Morbus Gaucher sowie ueber das Erscheinen der typischen Pigmentationen. Ann. paediat., 1938, 152: 87–94.
9. Donovan, E. J. Splenectomy in child 11 months of age for Gaucher's disease. Surg. Clin. N. America, 1931, 11: 517–520.
10. Epstein, Emil. Beitrage zur Chemie der Gaucherschen Krankheit. Biochem. Ztschr., 1924, 145: 398–414.
11. Erdmann, J. F., and Moorhead, J. J. Splenectomy for splenomegaly (Gaucher type). Am. J. M. Sc., 1914, 147: 213–224.
12. Gaucher, E. De L'épithélioma primitif idiopathique de la rate: hypertrophie sans leucémie. Thèse de doct., Paris, 1882.
13. Hoffman, S. J., and Makler, M. I. Gaucher's disease; review of literature and report of case diagnosed from section of inguinal lymph gland. Am. J. Dis. Child., 1929, 38: 775–793.
14. Horsley, J. S., Jr., Baker, J. P., and Apperly, F. L. Gaucher's disease of late onset, with kidney involvement and huge spleen. Am. J. M. Sc., 1935, 190: 511–518.
15. Hunter, D., and Evans, W. Gaucher's disease thirteen years after splenectomy. Proc. Roy. Soc. Med., 1929, 23: 224–225.
16. Mandelbaum, F. S. Two cases of Gaucher's disease in adults; a study of the histopathology, biology and chemical findings. Am. J. M. Sc., 1919, 157: 366–389.
17. Melamed, S., and Chester, W. Osseous form of Gaucher's disease; report of case. Arch. Int. Med., 1938, 61: 798–807.
18. Mueller, H. Ueber die sogenannten primaeren Lipoidosen. Ztschr. f. Kinderh., 1938, 59: 476–498.

19. MYERS, B. Gaucher's disease of lungs. Brit. M. J., 1937, 2: 8–10.
20. Idem. Gaucher's disease; splenectomy. Proc. Roy. Soc. Med., 1933, 26: 360–361.
21. PACK, G. T., and SILVERSTONE, S. M. Gaucher's disease; report of a case improved after splenectomy. Am. J. Surg., 1938, 41: 77–86.
22. PICK, L. Classification of diseases of lipoid metabolism and Gaucher's disease. Am. J. M. Sc., 1933, 185: 453–469.
23. Idem. Die Skelettform (ossuaere form) des Morbus Gaucher. Jena: Gustav Fischer, 1927.
24. PICOU and RAMOND. Quoted by Erdmann and Moorhead (11).
25. POOL, E. H. Gaucher spleen. Ann. Surg., 1921, 74: 635–37.
26. Idem. Discussion—Surgery of the spleen. Tr. Am. Surg. Ass., 1928, 46: 121–122.
27. POOL, E. H., and HIPSLEY, R. W. Effects and results of splenectomy in a variety of conditions. Surg. Clin. N. America, 1930, 10: 429–440.
28. POOL, E. H., and STILLMAN, R. G. Surgery of the Spleen. P. 230. New York: D. Appleton & Co., 1923.
29. POTTER, E. P., and MCRAE, C. C. Gaucher's disease; report of two cases with remission in one following administration of liver extract. Am. J. M. Sc., 1933, 185: 92–96.
30. ROWLAND, R. S., and STURGIS, R. H. Gaucher's disease. In: Practice of Pediatrics (Brennemann), 1937, 3: Chap. 23. pp. 61–80.
31. SPACKMAN and MACKIE. Quoted by Aballi and Kato (1).
32. ULLRICH, O. Splenektomiefolgen beim Morbus Gaucher. Ztschr. f. Kinderh., 1933, 55: 1–11.
33. VOGEL, P., and BASSEN, F. A. Sternal marrow of children in normal and in pathologic states. Am. J. Dis. Child., 1939, 57: 245–268.
34. WECHSLER, H. F., and GUSTAFSON, E. Gaucher's disease associated with multiple telangiectases in an elderly woman. N. York State J. Med., 1940, 40: 133.
35. WHIPPLE, A. O. Studies in splenopathy; introduction. J. Am. M. Ass., 1936, 107: 1775–1776.

EDITORIALS

SURGERY
Gynecology and Obstetrics

FRANKLIN H. MARTIN
Founder and Managing Editor
1905–1935

LOYAL DAVIS, EDITOR

Associates
SUMNER L. KOCH MICHAEL L. MASON

DONALD C. BALFOUR, *Associate, Editorial Staff*

APRIL, 1941

WAR MEDICAL SERVICE IN GREAT BRITAIN

THE success of the British fighting forces in opposing the Nazi Colossus has appealed to the imagination and sympathies of the American people to such an extent as to obscure the working of some of the machinery that made such achievements possible. The result alone seemed important and only a few bothered to lift the hood to look at the engine. Among the various essential parts of this mechanism is the medical organization, and it may be of interest to American doctors to learn something of how it is working and what it is accomplishing.

In the first place it is essential to point out that the medical corps of the army and navy are playing but a small part in medical relief work in Great Britain. In defensive preparations prior to the war the planning commissions envisaged the probability of large scale air raids on cities and industrial areas from the outbreak of the war and it was foreseen that the care of civilian casualties might be a more important problem for the medical organization than that of military casualties. In addition the civilian population would present other health problems growing out of the evacuation of refugees from the cities and the crowding together in public shelters of those who remained. So in addition to the medical corps of the army and navy and of the separate air force a fourth civilian organization known as the Emergency Medical Service or "E. M. S." for short was set up under the Minister of Health.

The responsibilities of these four different services are separate but related. The medical corps of the Royal Navy is the most nearly independent service and comes closest to doing what it was intended to do, namely care for the illnesses and casualties among the naval and fleet air arm personnel. It has its hospitals scattered about England and elsewhere, chiefly at the various naval bases. The writer visited one of these hospitals in October. It was situated in a coast city that was very exposed to air bombardment. The buildings were ancient and built in years when sail still provided the motive power of ships. The receiving and operating rooms were improvised in the subterranean vaults and were well organized. Each case was inspected on admission and tagged either to be sent to the resuscitation room, to the operating room via x-ray, or to the ward. Shock teams were organized to work in the resuscitation room and were able to draw on an ample blood bank and stores of plasma or dried serum obtained and prepared by the hospital. A number of severe burn cases were under treatment and apparently this is a not infrequent type of

naval casualty resulting either from fires or bursted steam pipes. It is to be noted that this hospital handled civilian casualties as well as those suffered by naval personnel. Because of its exposed position patients treated there had to be evacuated as soon as they were transportable and they were then sent on to an E. M. S. Hospital farther inland.

The Royal Army Medical Corps maintains only a few general hospitals in England, but does have a number of small camp hospitals where medical and minor surgical conditions are handled. A number of general hospitals were established in northern France during the time that the British Expeditionary Force was holding its sector at the front. Here too was assembled the best part of the fine motorized equipment organized for the medical and surgical care of the army in the zone of combat. These included mobile operating units, x-ray vans, laboratory and other cars. All of these were lost in the battles of Belgium and Northern France. The plans of medical organization called for the evacuation of the wounded from the army general hospitals to E. M. S. hospitals in England. These plans were put to a hard test in the evacuation of the wounded from Dunkirk. Most of the wounded had to be rushed from the place where they fell directly on board ship without receiving other than first aid treatment. Often it was several days before they reached their destination in hospitals in England. The difficulty of properly handling the wounded in the confusion of the embarcation and debarcation, with the well and injured hopelessly mixed may be well imagined. Yet somehow the authorities proved equal to the occasion and the wounded were sorted, loaded on hospital trains, and distributed all over England, for the main part to E. M. S. hospitals. Although many of the wounds proved badly infected and gas infection was common it was the general impression that the condition of the patients upon arrival was less bad than might have been anticipated. This was generally attributed to the widespread oral administration of sulfanilamide begun at the first aid post and continued throughout the journey. Although there was no opportunity for proper control of the drug by blood level determinations and the dosage had to be regulated according to the judgment of the different doctors who were in charge, still the effect in general was beneficial and undoubtedly played a part in preventing many of the more virulent types of infections.

The Royal Air Force, being an independent service, maintains its own separate hospitals for the treatment of its officers and men. Because of the importance from the standpoint of national defense of restoring flying personnel to service as rapidly as possible, special facilities were arranged for the prompt transfer of these men from other hospitals where they might be taken immediately after injury to the special R. A. F. hospitals where a staff of specialists was assembled and all facilities provided to bring about as quick a recovery as possible. Not all patients were transferred, however, and exception was made when the patients required special treatment which could be best obtained at other hospitals. This was the case with the burned aviators who were treated at special faciomaxillary centers maintained by the Emergency Medical Service under the direction of the distinguished plastic surgeon, Sir Harold Gillies.

Severe burns of the face and hands proved a common type of injury among aviators whose planes were set on fire in aerial combat. During the process of getting out of the cockpit in order to bail out by parachute their faces and hands were exposed to the flames while their bodies were relatively protected by their heavy flying costumes. These men were ter-

ribly disfigured and frequently required complete reconstruction of nose, mouth, and eyelids in addition to skin grafts to the face. Such operations must be done in different stages over a period of many months, but beautiful work is being done and they are being made fit again to return to human society. The burns of the hands also represented a difficult problem requiring co-operative effort from both plastic and orthopedic surgeons to achieve the best results. The study of these cases, the majority of which were treated in the beginning by tanning of the necrotic tissue with various solutions, led to the important conclusion that without prejudice to the use of tanning in other parts of the body, in the case of the face and hands it caused excessive tissue loss and scar formation and should be abandoned. An order to this effect was issued to the R. A. M. C. and E. M. S. hospitals.

The Emergency Medical Service in the Ministry of Health is the new organization developed to meet the special conditions that were expected to arise in this war. It is entirely civilian and there is no uniform. It admits to its hospitals for treatment first, any disease or injury arising in or incurred by personnel of the military forces whether army, navy, or air force; second, civilians with injuries incurred as a result of enemy action or in the course of civil defense; and third, civil cases of any character that have to be sent in on account of the necessities of war, as for example the evacuation of a hospital that has been subjected to aerial bombardment.

At the outbreak of the war the E. M. S. constructed or improvised a large number of hospitals throughout England. For the most part these were mental hospitals which were evacuated of their patients and converted to general medical and surgical use, or hut hospitals built usually about a nucleus of preexisting buildings which supplied power and service. The administration is regional under hospital officers and group officers. These men are responsible for supplying staff and personnel and also for the transportation and distribution of the convoys of sick and wounded who must be evacuated from regions threatened with aerial bombardment.

The city of London is divided into six or seven sectors shaped like a section of pie each with its apex extending into the central part and including one of the important teaching hospitals such as Guy's, St. Bartholomew's, St. Mary's, St. Thomas', etc., which is supposed to control the whole sector. The sector stretches peripherally for a considerable distance, and its base may be as much as 50 miles distant from its peak. A number of E. M. S. hospitals are included in each sector and theoretically these hospitals are staffed by doctors and nurses from the dominating hospital and medical school at the apex. This is in order that these hospitals may work together with the minimum of friction and that all of them may be utilized in the education of medical students and nurses. The medical staffs of the E. M. S. are all in the employment of the Ministry of Health and for the most part on a full time basis, although some are on half time. The salaries are meager, ranging from 500 pounds for a junior physician or surgeon to 800 pounds for a senior with an additional allowance of 100 pounds for living expenses. It may be remarked in passing that private practice is so completely disrupted in London and many of the other large cities that many of the doctors are completely dependent on these salaries for their living.

Because of the constant threat of air bombardment a large number of the beds in the central hospitals must be kept empty. This is both for the protection of patients and also to provide facilities for the reception of the large numbers of air raid casualties that might

be produced at any moment by an unlucky hit. Most of the important hospitals in London have sustained severe damage from bomb hits and it is estimated that it will be necessary to replace the entire hospital plant of London at the end of the war. Emergency operating and nursing facilities have been organized in the basements of these hospitals and here are treated the ordinary urgent civilian conditions as well as the air raid casualties. Only small staffs of doctors and nurses are maintained. As quickly as possible the patients are evacuated and transported to the more outlying hospitals in the respective sectors where their security will be greater than in central London and better care can be given.

All of these hospitals are regularly supplied with citrated blood, plasma, and dried serum from one of the four blood depots organized by a committee of the Medical Research Council. In the American section of the Park Prewett Hospital at Basingstoke the blood depot supply truck called regularly every Monday and delivered twelve half liters of blood and took away the unused remainder of the blood that had been left from the previous week, to be converted into plasma. The blood supply service also replenished the stock of plasma and dried serum and kept it up to an agreed level. This was a fine service and was available to all those hospitals which requested it.

Finally in any comment upon the medical organization in England one must pay tribute to the fine spirit of devotion and sacrifice of the doctors and nurses. These men and women have faced the dangers and miseries of air raids without complaint. Many have been killed or wounded. They have never stinted their services in furnishing medical and nursing care and in times of danger have remained with their patients and tried to provide for their protection. Their spirit has been typical of the English people as a whole and they have faced every trial with a jest. Frequently when I encountered a British medical colleague he would remark quite casually and as if it were a great joke that he had received news that his house in London had been hit by a bomb. Although this generally represented the loss of all that had been collected during a life time none of them wanted sympathy. But if one explored the matter further one might elicit some poignant remark such as "Well it is rather hard on my wife because she is too old to start all over again." One returns to the United States with the feeling that we Americans may take pride in our British heritage.

PHILIP D. WILSON.

THE SURGEON'S LIBRARY

REVIEWS OF NEW BOOKS

IN the first chapter of *Gynecological and Obstetrical Pathology*[1] the author gives a brief review of the endocrinology of the menstrual cycle and pregnancy, and calls attention to the histological changes produced by the hormones involved.

Each subsequent chapter starts with a short description of the normal histology of the particular part to be considered which is in turn followed by a description of the pathological changes. Brevity and conciseness characterize the descriptions throughout the book; however, each phase of pathology is alloted its proper consideration.

The book contains 495 pages and 42 well chosen illustrations. All the illustrations, but one, are in black and white. A bibliography is presented at the end of each chapter. This treatise is a very valuable reference for the student or practitioner of gynecology.

CHESTER C. DOHERTY

FOUNDATIONS for further research in neurohistology have been laid in the 164 page monograph of Professor Boeke.[2] The book is divided into four chapters which cover: (1) innervation of skin, (2) the sympathetic ground plexus, (3) the relation of sympathetic interstitial cells to neurons and to humoral phenomena, and (4) a critical discussion of the neuron doctrine. The general objective of the work is the correlation of physiologic and histologic observations. In his study of regeneration of nerves to the skin, the author was not able to confirm Head's theory that protopathic sensibility was mediated by nerves of the sympathetic system, but found that such sensibility was a phase associated with regeneration of somatic nerves. Numerous examples are cited to show the widespread distribution of the sympathetic ground-plexus to all parts of the body. Interstitial cells are discussed with reference to their possible functions and the meaning of their presence in higher vertebrates to phylogenetic development as traced from invertebrates through *Amphioxus* and the sharks. The final chapter is devoted to pointing out some of the inadequacies of the neuron doctrine as it exists in its classical form, and a plea is made to regard synapses as living membranes which possess physiologic continuity. The syncytial character of many nerve plexuses is regarded to be out of harmony with the idea of strict discontinuity of individual neurites. The author states frankly that the treatise is colored by his own opinions, but that much of the material deals with controversial subjects in which it is often better to leave a question open than to draw unwarranted conclusions.

The book is better suited to the needs of the more advanced student in neurohistology or neurophysiology than it is to those of the beginner, because the author presupposes a knowledge of the literature on the part of the reader. It also should be very readable to the clinical neurologist. There are 48 text figures and a bibliography of 88 references. Some figures are taken from older works (as far back as 1894), but most of them are relatively new. The bibliography is representative rather than exhaustive.

HAROLD A. DAVENPORT

THE approach to the diagnosis of "the acute abdomen" by Cope[3] is essentially a clinical one. A composite picture that includes the phenomena of pain, tenderness, rigidity, nausea and vomiting, and the localizing phenomena, plus such systemic signs as fever, pulse increase, and leucocytosis, is present with certain variations in all types of the acute picture. Clinical experience and judgment, with a discernment for shadings, enable us to differentiate, for instance, acute appendicitis from acute salpingitis, cholecystitis, or other lesions. This approach and clear appraisal of clinical symptoms is excellently accomplished in this compact volume now in its eighth edition.

The subject matter is contained under the following chapter headings: principles of diagnosis in acute abdominal diseases, methods of diagnosis, appendicitis, perforation of gastroduodenal ulcer, acute pancreatitis, acute abdominal obstruction, intussusception, carcinoma of the colon, strangulated hernia, ectopic gestation, cholecystitis. There are other additional chapters on the colics, abdominal injuries, abdominal disease with genito-urinary symptoms, acute peritonitis, and diseases which simulate an acute abdomen.

The author has wisely made the chapter discussing appendicitis the most extensive, as well as a pivotal point for differential diagnosis. The chapter is undoubtedly the best of the group. There is little room for fundamental difference of opinion with ideas expressed by the author. The clinical picture of each disease is well drawn and excellently written. One minor criticism might be ventured; namely, the presentation of perforated ulcer in clinical "stages."

[1] GYNECOLOGICAL AND OBSTETRICAL PATHOLOGY; WITH CLINICAL AND ENDOCRINE RELATIONS. By Emil Novak, A.B., M.D., D.Sc. (Hon. Dublin), F.A.C.S. Philadelphia and London: W. B. Saunders Co., 1940.

[2] PROBLEMS OF NERVOUS ANATOMY. By J. Boeke, LL.D. (Glasg.). 1st ed. London: Oxford University Press 1940.

[3] OXFORD MEDICAL PUBLICATIONS. THE EARLY DIAGNOSIS OF THE ACUTE ABDOMEN. By Zachary Cope, B.A., M.D., M.S.(Lond.), F.R.C.S. (Eng.). 8th ed. London: Oxford University Press, 1940.

This work is a handy volume; it is accurate, complete, and groups acute diseases of the abdomen in one volume.

J. R. BUCHBINDER.

THE volume *Surgery of the Alimentary Tract* by Devine[1] is a large one, as might be surmised from its title. It is divided into four sections: (1) the diagnosis of surgical dyspepsia; (2) the surgery of surgical dyspepsia and of the upper part of the abdomen; (3) abdominal emergencies which may involve either the upper or the lower part of the abdomen; and (4) surgery of the lower part of the abdomen.

In the first section the author has made an unusual and instructive approach in a thorough discussion of the dyspepsias, both gastroduodenal and extragastric, or reflex. A thorough and sound exposition of the mechanism and correlated clinical picture is given. A wide section is devoted to ulcer—gastric, duodenal, and jejunal ulcer—duodenal diverticulum, gastritis and duodenitis, and carcinoma.

The second section of part one of the text deals with "precision" methods of diagnosis, chiefly x-ray, and includes a chapter on the gastroscope.

Under "surgical procedures" there is an extensive and well illustrated section dealing with the operative surgery of the stomach, duodenum, bile tracts, pancreas, and spleen, as well as a section on postoperative complications. On the operative management of duodenal ulcer the author is less radically inclined than continental surgeons and perhaps less so than most American surgeons. In the "infective" type of ulcer he employs gastro-enterostomy; in the "acidic" type, partial gastric resection, his feeling being that in the ulcer of his peoples the "infective" type predominates. A considerable amount of space is devoted to the technique of resection for both ulcer and carcinoma, and there are a tremendous number of excellent illustrations—far more than are usually found in a text on gastroduodenal surgery.

In the fourth section are included appendicitis, carcinoma of the colon and rectum, and diverticulitis.

One cannot but be impressed by the obvious experience of the author, as shown by the abundance of careful descriptive detail and illustrations, in the preparation, approach, and performance of operations. The work represents a fine contribution to the surgical dyspepsias, and particularly it is an excellent reference volume for the surgeon interested in the surgery of the stomach and duodenum.

J. R. BUCHBINDER.

IN the revised edition of Professor Grant's *A Method of Anatomy, Descriptive and Deductive*[2] an introductory section on the bodily systems has been added to the text material, and over 100 figures added to the original list of illustrations—making a present total of 651. Many of the new figures are less diagrammatic and are therefore better representations of dissections than were those of the original edition.

The first section deals, in general terms, with the several bodily systems. Osseous structure is considered microscopically; bones are classified; the significance of markings discussed—vascular foramina, elevations, facets, and foveae. Muscles are described on the basis of internal fascicular architecture, and the physiological mechanism of contractions is described in simple terms. The vascular system is considered from many standpoints: as to the volume of blood contained in the body; as to the character of arteriovenous anastomoses; as to special nature of sinusoids, end-arteries, and cavernous tissue. Many helpful facts are recorded regarding vascular patterns in such special areas as nail-bed and lip, cerebrum and spleen, erectile bodies; topographically different parts are thus catalogued together on the basis of peculiarity in blood supply. By this means the student is introduced to a rationalizing scheme of study. The nervous, digestive, respiratory, urinary, and reproductive systems are similarly treated in this preliminary section.

The regional accounts follow, a section being devoted to each of the major subdivisions of the body, namely, upper limb, abdomen, pelvis and perineum, lower limb, thorax, head and neck. A closing section covers the autonomic nervous system, body types, the separate elements of the skeleton.

Throughout these sections the anatomical detail is presented with admirable ingenuity; simple mechanical principles, homely physical notions are abundantly cited in order to make structural facts familiar and, therefore, mentally manageable. Thus, in discussing the musculature, the attachments of the upper limb to the head are likened to guy ropes; the looseness of the pectoral fascia is explained as adaptive to free thoracic movement during respiratory activity; marginal thickening of the scapula is said to prevent buckling of that bone when the serratus anterior pulls upon the inferior border; the carpal bones are presented as modified blocks, altered from cubical to various other forms.

In the section about the abdomen the inguinal canal is likened to a channel whose roof consists of 3 arcades contributed by the trilaminar wall; it is pointed out, strikingly, that the abdominal viscera lie, largely, within the thorax cage (because of height of diaphragm) and within the pelvic bowl; the liver is described as resembling an oblong block; the intestine with its mesentery, the kidneys with their retroperitoneal stratum are likened to 3 pages of a book, comparatively movable after dissection.

In the section dealing with the anatomy of the lower limb, complex anatomy is again simplified by comparison with common objects; the space of the femoral triangle, with its continuation as adductor canal, is likened to a funnel with a long spout; the weight-bearing points of the foot suggest the supportive mechanism of a tripod. The chapter con-

[1] THE SURGERY OF THE ALIMENTARY TRACT. By Sir Hugh Devine, M.S., F.R.A.C.S., F.A.C.S. Baltimore: The Williams & Wilkins Co., 1940.

[2] A METHOD OF ANATOMY, DESCRIPTIVE AND DEDUCTIVE. By J. C. Boileau Grant, M.C., M.B., Ch.B., F.R.C.S.(Edin.). 2d ed. Baltimore: The Williams & Wilkins Co., 1940.

tains tables of muscle action groups and time tables of epiphyseal development.

The section on thoracic anatomy, in addition to dealing with the regular segregated items, discusses such varied general topics as posture, alteration in form of the bronchial tree, development of the heart and great arteries.

The section on the anatomy of the head and neck is, like the preceding sections, replete with diagrammatic figures. Some of these are cryptic and would require an experienced student's knowledge for full understanding. Others are better representations of dissections or of gross sections, and are, therefore, distinctly helpful.

Professor Grant's *Method of Anatomy* resembles a manual more closely than it does any other type of treatise, but it differs from the standard manual in presenting concepts superabundantly. It is not a textbook of the regular systematic order, the bulk of its content being arranged upon a regional basis. The volume is not a substitute for an atlas, since the drawings are diagrammatic; it is not a dissector's guide, but is now accompanied by a small companion volume which serves the student in the latter capacity.

This book, which is essentially a manual of regional anatomy filled with concepts, is unique in its attempt to teach anatomy in such a way that underlying principles, rather than mere facts, are made its chief content. Certainly only a gifted teacher could formulate as many valuable notions as Professor Grant has included in his volume. His experience has allowed him to furnish some of the cleverest bits of description yet encountered in anatomical writings. But in the commendable desire to clarify and to simplify, some important details of anatomy are omitted; simplification becomes so demanding that what remains of fundamental description is actually quite "traditional."

Professor Grant's provocative volume could scarcely replace any regular part of the student's anatomical library, but it could, with great profit, be added to such a library. For the graduate student its content would be inspiring; the surgical anatomist could profitably employ it as a source book for lecture material; and it would carry the young teacher glowingly through those beginning years which, customarily, are depressingly didactic. BARRY ANSON.

THE author of *The Injured Back and Its Treatment*[1] does not claim that the content of this book is new. For those who have kept abreast of modern developments in trauma and diseases of the spine, it is intended as a compilation of modern concepts in this field and as a bibliography in which all important related work is made available. For those whose attitude toward back pain is one of fear and helplessness, a complete and concise course in the anatomy, pathology, physiology, diagnosis, and treatment of any related condition is available. For the practitioner who for the first time sees the patient with a lesion of the spine or its related structures, the chapter on the routine examination of the back should prove most valuable, for it is the guide by which he may evaluate the patient's complaints, discard the irrelevant, and localize those factors playing a major rôle in the clinical picture. The editor has wisely refrained from accentuating those lesions which are amenable to operative management alone. The prolapsed intervertebral disc and other causes of cord and nerve compression are discussed but with the reserve warranted by their relative infrequency.

This book has been published at an opportune time. It is alone in the field and is a "must" number for the medical library. J. K. STACK.

[1] THE INJURED BACK AND ITS TREATMENT. Edited by John D. Ellis, M.D. Springfield, Ill., and Baltimore, Md.: Charles C. Thomas, 1940.

NOT only have Lowsley and Kerwin[2] amplified and enlarged their original textbook on urology to a two volume work but they have succeeded in compiling one of the most comprehensive and valuable editions on this subject which has appeared in recent years. While the book is written primarily for the medical student, the general practitioner, and the general surgeon, it also provides a completely up-to-date reference work for the trained urologist.

General diagnostic procedures, with special emphasis on their practical value, are considered in great detail in the early text. Roentgenography of the genito-urinary tract is adequately considered and well illustrated. This is followed by an excellent chapter on anesthesia in urology. Embryology, anatomy, anomalies, and physiology of each division of the male genito-urinary, and the female urinary, organs are fully described before injuries and diseases are discussed. The most outstanding feature of this work is the very complete consideration of treatment of all urologic diseases and anomalies. The excellence of the illustrations by Didusch clarifies each surgical procedure, making the work an atlas of urologic surgery in addition to the text. A full and complete bibliography is appended to each chapter.

This work can be most heartily recommended, not only as a textbook, but as a suitable reference which covers the entire field of modern urology.

VINCENT J. O'CONOR.

IN the latest revision of their book about diseases of infancy and childhood, Drs. Holt and McIntosh[3] acknowledge the inability of any one or two authors to write with authority on such a broad specialty as pediatrics. Increasing specialization within the pediatric field has enabled investigators to acquire information and experience which it is impossible for the general pediatrician to obtain.

[2] CLINICAL UROLOGY. By Oswald Swinney Lowsley, A.B., M.D., F.A.C.S., and Thomas Joseph Kirwin, M.A., M.S., M.D., F.A.C.S. Vols. 1 and 2. Baltimore: The Williams & Wilkins Co., 1940.

[3] HOLT'S DISEASES OF INFANCY AND CHILDHOOD; A TEXTBOOK FOR THE USE OF STUDENTS AND PRACTITIONERS. By the late L. Emmett Holt, M.D., and John Howland, M.D. Revised by L. Emmett Holt, Jr., M.D., and Rustin McIntosh, M.D. 11th ed. New York and London: D. Appleton-Century Co., 1940.

On this account the writers have enlisted the aid of some thirty of their colleagues who have collaborated in certain features of the work. By this means the authors have been able to maintain uniformity of style and presentation, and at the same time to take advantage of the special studies of workers in some particular branch of pediatrics.

The result is a textbook which presents in admirable fashion the essentials of present day pediatric knowledge. Several sections of the book have been entirely rewritten, and others extensively revised and enlarged to bring the subject matter up to date.

This book can be heartily recommended both to students and practitioners. STANLEY GIBSON.

THE volume *Physiology of the Fetus* by Windle,[1] comprising a modest 226 pages, is packed with well indexed and tabulated information bearing strictly on the title. It covers in considerable detail such matters as the function of the fetal circulation, blood, respiration, digestion, elimination, endocrines, the neuromuscular system, and sensation.

The obvious difficulties entailed in the investigation of such fetal functions limit the subject matter to a great extent. Yet it was astonishing to one not intimately associated with such research, to find how much practical knowledge is actually at hand. The author has gathered together his material in a concise and logical manner, has added to it his own considerable number of observations, and has discussed controversial points in a constrained and enlightening manner. At the same time the book makes interesting reading and is not stilted. His is a timely subject which, together with similar work on fetal pathology, should speed the time when we shall consider a diagnosis of death from prematurity entirely inadequate. More information of this sort should help the pediatrist to understand better and to treat more successfully many common problems of the newly born, such as asphyxia and cyanotic attacks.

In one respect, however, the reviewer found himself unsatisfied. At the end of each chapter he felt a great curiosity to know just what Dr. Windle thought about the practical implications of his research. This feeling is mentioned not at all in criticism, but in the hope that future editions may be enriched by his seasoned judgment on the many questions which come to mind. This sort of correlation between research and clinical needs is nowhere more essential than in the care of the premature and newly born infant. This volume should be "must" reading for pediatrists as well as for students and investigators in the field. C. ANDERSON ALDRICH.

[1] PHYSIOLOGY OF THE FETUS; ORIGIN AND EXTENT OF FUNCTION IN PRENATAL LIFE. By William Frederick Windle. Philadelphia and London: W. B. Saunders Co., 1940.

CORRESPONDENCE

RADICAL CURE OF HYDROCELE BY EXCISION OF SEROUS LAYER OF SAC

To the Editor: In the issue of SURGERY, GYNECOLOGY AND OBSTETRICS for April, 1940, a new operation for the radical cure of hydrocele by excision of the serous layer of the sac is described by Hugh Young, of Baltimore.

I have been doing this operation in Madras and now in Delhi for about six years. It is the routine radical operation which I have practised and taught to my students for that time. I am sure Dr. Young will be interested to know this and at the same time excuse the liberty which I take in pointing it out I do so in no critical spirit, remembering that hemorrhage probably drove me to get down to the serous layer.

M. M. CRUICKSHANK.
Lt. Col., Indian Medical Service

Delhi, India